09/185732

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.10

APPLICANTS:	BARROWS, et al
TITLE:	ADHESIVE SEALANT COMPOSITION
PATENT NO.:	RE38,158
ATTORNEY REF:	136071.00016
DATE OF DEPOSIT:	April 8, 2010
EXPRESS MAIL NO.	EV472066223US

I HEREBY CERTIFY THAT THIS SUBMISSION OF:

☒ SUPPLEMENT TO APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. § 156 WITH LETTER DATED APRIL 5, 2010 FROM 3M TO NEOMEND (3 PAGES) – (ORIGINAL AND 2 COPIES); AND

☒ POSTCARD

IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE VIA UNITED STATES POST OFFICE EXPRESS MAIL UNDER 37 C.F.R. § 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO MAIL STOP HATCH-WAXMAN PTE, COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450.

Paula J. Watson
(Typed or printed name of person mailing paper or fee)

Paula J Watson
(Signature of person mailing paper or fee)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: RE 38,158	)
Inventors: Barrows, et al.	) EXPRESS MAIL NO.:
Assignee: Neomend, Inc.	) EV472066223US
	)
Issued: June 24, 2003	)
Title: ADHESIVE SEALANT COMPOSITION	)

Atty. Docket No. 136071.00016

Customer No. 21269

Mail Stop: Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENT TO APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. § 156

Dear Commissioner:

On March 2, 2010, Applicant, Neomend, Inc. ("Neomend"), owner of U.S. Reissued Patent No. RE38,158 (the "'158 Patent"), submitted an Application for Patent Term Extension Under 35 U.S.C. § 156 through its duly authorized agent named below.

At this time, Neomend wishes to supplement its application with the attached Letter from 3M Company ("3M"), d/b/a 3M Health Care and 3M Innovative Properties Companies, to Neomend dated April 5, 2010. In its Letter, 3M authorizes Neomend to seek an application for an extension of the patent term on the '158 Patent and rely at least in part upon the activities of 3M before the Federal Food and Drug Administration ("FDA"). The product covered by the '158 patent was subject to a regulatory review and subsequently approved by the FDA under PMA No. P010047, IDE No. G980283.

As required by 37 C.F.R. § 1.740(b), this supplement to the application for patent term extension under 35 U.S.C. § 156, including its attachment, is being submitted as an original and two duplicate copies thereof.

Please direct all inquires, questions and correspondence regarding this supplement to the undersigned.

The Director is hereby authorized to charge any additional fees which may be required for this submission or credit any overpayment to Deposit Account No. 50-0436.

Respectfully submitted,

N. Nicole Endejann, Reg. No. 50,229 and
Raymond A. Miller, Reg. No. 42,891

PEPPER HAMILTON LLP
One Mellon Center, 50th Floor
500 Grant Street
Pittsburgh, PA 15219
Phone: (412) 454-5869
Fax: (412) 281-0717
E-Mail: millerra@pepperlaw.com
Date: April 8, 2010

3M Health Care Business
3M Infection Prevention

3M Center, Bldg. 0275-04-E-01
St. Paul, MN 55144-1000
651 733 1110

3M

April 5, 2010

David M. Renzi
President and CEO
Neomend, Inc.
60 Technology Drive
Irvine, California 92618

Re: Neomend, Inc. – U.S. Reissued Patent No. RE38,158
Application for Extension of Patent Term under 35 U.S.C. § 156

Dear Mr. Renzi:

Congratulations on the recent approval by the Federal Food and Drug Administration (FDA) in the United States of Neomend's PMA No. P010047 for ProGel™ Pleural Air Leak Sealant on January 14, 2010. This letter confirms our understanding that the PMA No. P010047 was originally submitted by 3M Company on October 30, 1998 and references IDE No. G980283.

This letter also confirms that, in the event an extension of U.S. Reissued Patent No. RE38,158 ("the '158 Patent") now assigned to Neomend, Inc., under 35 U.S.C. §156, based on agency review to approve commercialization of ProGel™ Pleural Air Leak Sealant, may be obtained, 3M, and its affiliates and predecessors, including 3M Company, d/b/a 3M Health Care, and 3M Innovative Properties Company , (hereinafter "3M") hereby authorizes Neomend, Inc. to seek an application for an Extension of the patent term of its '158 Patent, relying at least in part upon the activities of 3M before the FDA.

Very truly yours,

Mark Schroer
Vice President – Business Development
3M Infection Prevention Division

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.10

APPLICANTS:	BARROWS, et al
TITLE:	ADHESIVE SEALANT COMPOSITION
SERIAL NO.:	RE38,158
ATTORNEY REF:	136071.00016
DATE OF DEPOSIT:	March 2, 2010
EXPRESS MAIL NO.	EV472068065US

I HEREBY CERTIFY THAT THIS SUBMISSION OF:

☒ TRANSMITTAL LETTER (4 PAGES)

☒ APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. § 156 (21 PAGES) WITH EXHIBITS A – W (ORIGINAL AND 2 COPIES)

☒ CHECK NO. 09852 IN THE AMOUNT OF $1,120.00

☒ POST-CARD

IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE VIA UNITED STATES POST OFFICE EXPRESS MAIL UNDER 37 C.F.R. § 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO MAIL STOP HATCH-WAXMAN PTE, COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450.

Paula J. Watson
(Typed or printed name of person mailing paper or fee)

Paula J. Watson
(Signature of person mailing paper or fee)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: RE38,158	)	
Inventors: Barrows, et al.	)	
Assignee: Neomend, Inc.	)	EXPRESS MAIL NO.:
	)	EV472068065US
Issued: June 24, 2003	)	
Title: ADHESIVE SEALANT COMPOSITION	)	

Atty. Dkt. No. 136071.00016

Customer No. 21269

Mail Stop: Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Being filed herewith are the following papers:

1. Application for Extension of Patent Term Under 35 U.S.C. § 156;

2. Exhibit A - Approval Letter from the Food and Drug Administration ("FDA") dated January 14, 2010 for ProGel™ Pleural Air Leak Sealant;

3. Exhibit B - U.S. Reissued Patent No. RE38,158;

4. Exhibit C - Certificate of Correction issued by the United States Patent and Trademark Office ("U.S.P.T.O.") on April 6, 2004 for U.S. Reissued Patent No. RE38,158;

5. Exhibit D - Maintenance Fee Payment record retrieved from the U.S.P.T.O. database relevant to U.S. Reissued Patent No. RE38,158;

6. Exhibit E – Internal Quality Program document entitled Functional Testing – Surgical Sealant Kits (Document #: QP-0002 Rev. C);

7. Exhibit F –FDA approved labeling, Package Insert, Document M-0005 Rev. B for ProGel™ Pleural Air Leak Sealant;

8. Exhibit G – Chemistry Specification (Document Number: CS-78-8110-3494-7, Revision C);

9. Exhibit H – IDE conditional approval letter from the FDA dated June 29, 1999;

10. Exhibit I – PMA acceptance letter from the FDA dated August 23, 2001;

11. Exhibit J - Table listing the significant activities undertaken by the marketing Applicant, or its predecessor(s), during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities;

12. Exhibit K – Letter to the FDA dated June 25, 2007 notifying the FDA of the transfer of ownership of PMS No. P010047 from 3M to Neomend;

13. Exhibit L - FDA's letter acknowledging the change is ownership and accepting removal of the first Directed Hold dated June 27, 2007;

14. Exhibit M – Assignment recorded with the U.S.P.T.O. on July 27, 1994 at Reel 007123, Frame 0460;

15. Exhibit N – Assignment recorded with the U.S.P.T.O. on November 4, 1998 at Reel 009564, Frame 0154-0155

16. Exhibit O - Assignment recorded with the U.S.P.T.O. on September 10, 2004 at Reel 015116, Frame 0336-0337;

17. Exhibit P – Assignment recorded with the U.S.P.T.O. on August 20, 2009 at Reel 023119, Frame 0699-0704;

18. Exhibit Q – Cover Letter for 3M's IDE Final Report to the FDA dated October 11, 2001 (one (1) page);

19. Exhibit R – Letter to FDA requesting First Directed Hold submitted April 19, 2004;

20. Exhibit S - FDA's letter accepting first Directed Hold dated April 20, 2004;

21. Exhibit T – Letter to FDA requesting Second Directed Hold submitted October 4, 2007;

22. Exhibit U - FDA's letter accepting second Directed Hold dated October 10, 2007;

23. Exhibit V – Letter to FDA requesting removal of Second Directed Hold submitted November 1, 2007 (one (1) page); and

24. Exhibit W - FDA's letter accepting removal of the second Directed Hold dated November 2, 2007.

Inquiries and correspondence relating to the enclosed application for patent term extension are to be directed to:

Raymond A. Miller
Attorney at Law/Patent Counsel
Reg. No. 42,891
Pepper Hamilton LLP
50th Floor
500 Grant Street
Pittsburgh, PA 15219-2502
412.454.5813 - Direct
412.281.0717 - Fax
866.422.3847 - Direct Fax
Email: millerra@pepperlaw.com

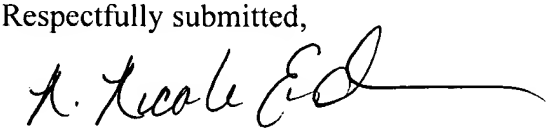
If any further information is required, please advise Mr. Miller at the above address.

ATHORIZATION

Pursuant to 37 C.F.R. § 1.20(j), a check for the application fee in the amount of $1,120.00 is enclosed with this application.

Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of the same, the Director is hereby authorized to charge Deposit Account No. 50-0436 for any such fees. Should a refund of fee paid be necessary, the Director is hereby authorized to credit any such amount to Deposit Account No. 50-0436.

Respectfully submitted,



N. Nicole Endejann, Reg. No. 50,229 and
Raymond A. Miller, Reg. No. 42,891

PEPPER HAMILTON LLP
One Mellon Center, 50th Floor
500 Grant Street
Pittsburgh, PA 15219
Phone: (412) 454-5869
Fax: (412) 281-0717
Date: March 2, 2010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: RE 38,158	)
Inventors: Barrows, et al.	) EXPRESS MAIL NO.:
Assignee: Neomend, Inc.	) EV472068065US
	)
Issued: June 24, 2003	)
Title: ADHESIVE SEALANT COMPOSITION	)

Atty. Docket No. 136071.00016

Customer No. 21269

Mail Stop: Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. § 156

Dear Commissioner:

This is an application for extension of patent term for U.S. Reissued Patent No. RE38,158 pursuant to 35 U.S.C. § 156 and 37 C.F.R. § 1.740. The applicant, Neomend, Inc. ("Neomend"), is the owner of U.S. Reissued Patent No. RE38,158, and is submitting this application by its duly authorized agent named below. Neomend's corporate headquarters is located at 60 Technology Drive, Irvine, California 92618.

The information required under subsections (1) to (15) of 37 C.F.R. § 1.740(a) is set forth in detail below. As required by 37 C.F.R. § 1.740(b), this application for patent term extension under 35 U.S.C. § 156, including its attachments, is being submitted as an original and two duplicate copies thereof.

(1) **A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics, 37 C.F.R. § 1.740(a)(1);**

The approved product is Neomend's ProGel Pleural Air Leak Sealant for application to visceral pleura during an open thoracotomy after standard visceral pleural closure with, for example, sutures or staples, of visible air leaks (≥2 mm) incurred during open resection of lung parenchyma. The Food and Drug Administration ("FDA") Classification Name is "Sealant, Polymerizing" under the FDA product code "NBE." The approved product is marketed as "Neomend ProGel™ Pleural Air Leak Sealant" or alternatively under the trademarked name "ProGel™." Neomend ProGel™ Pleural Air Leak Sealant is a single use device intended for application to visceral pleura during an open thoracotomy after standard visceral pleural closure with, for example, sutures or staples, of visible air leaks (≥2 mm) incurred during open resection of lung parenchyma.

Neomend ProGel™ Pleural Air Leak Sealant is a single-use medical device that is formed as a result of mixing two components: (i) a solution of human serum albumin (HSA) and (ii) a synthetic cross-linking component of polyethylene glycol ("PEG") that is functionalized with succinate groups. Upon mixing, a flexible hydrogel is formed.

Neomend ProGel™ Pleural Air Leak Sealant is supplied as a sterile, single-use two (2) component kit which, when mixed, makes a 4 ml total sealant volume for application to visceral pleura as an adjunct to standard visceral pleural closure of visible air leaks incurred during resection of lung tissue. The kit includes:

One (1) - Chemistry Kit –

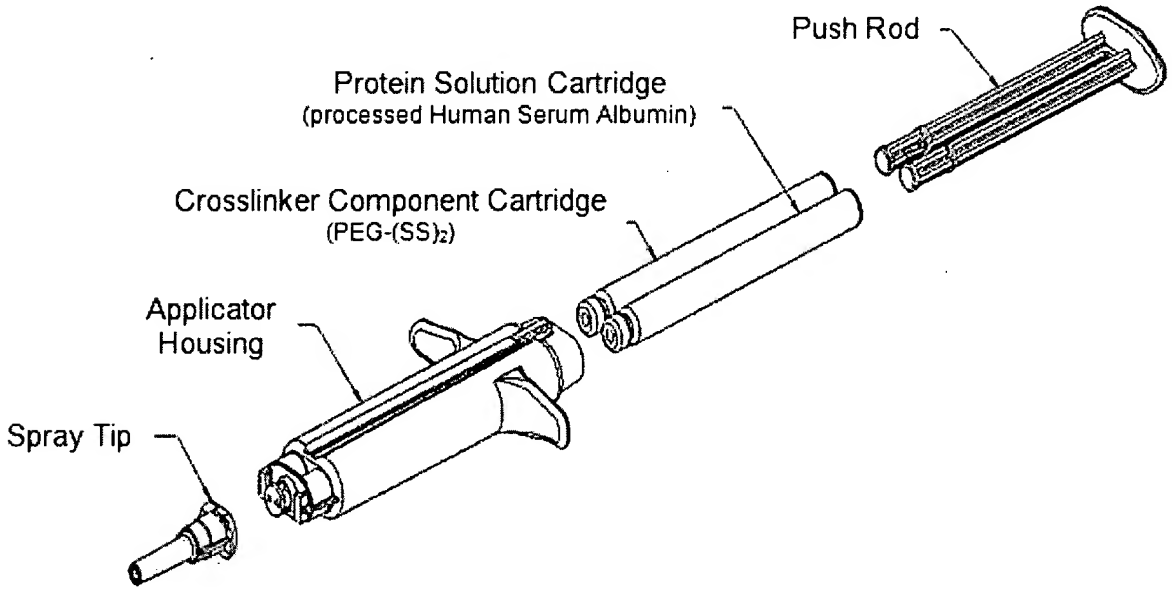
- One (1) – pre-loaded cartridge containing 2 ml of Protein solution (processed Human Serum Albumin)
- One (1) – pre-loaded cartridge containing Polyethyleneglycol di-succinimidyl succinate ((PEG-(SS)2)) as a dried white powder

One (1) – Applicator Kit –

- One (1) – 3 ml plastic syringe with 0.5 inch 26 gauge needle
- One (1) – 5 ml vial of USP sterile water for injection (2 ml to be used to reconstitute PEG-(SS)2)
- One (1) – Applicator assembly
- Two (2) – Spray tips

One (1) – Instructions for Use (Labeling)

FIGURE 1 ProGel™ PLEURAL AIR LEAK SEALANT DELIVERY SYSTEM
(STERILE WATER AND SYRINGE NOT SHOWN)



(2) **A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred, 37 C.F.R. § 1.740(a)(2);**

The Federal statute under which regulatory review took place for Neomend ProGel™ Pleural Air Leak Sealant is Section 515 (i.e., 21 U.S.C. §360(e)) of the Federal Food, Drug, and Cosmetic Act ("FDCA") and Section 520 (i.e., 21 U.S.C. § 360(j)) of the FDCA.

(3) **An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred, 37 C.F.R. § 1.740(a)(3);**

The Neomend ProGel™ Pleural Air Leak Sealant was approved for marketing on January 14, 2010. A copy of the approval letter from the FDA dated January 14, 2010 is attached hereto as **Exhibit A**.

(4) **In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved, 37 C.F.R. § 1.740(a)(4);**

Applicant notes that Neomend ProGel™ Pleural Air Leak Sealant was approved as a medical device under Sections 515 and 520 of the FDCA, as stated above in Section (2). Accordingly, Applicant believes that information referenced by 31 C.F.R. § 1.740(a)(4), which specifies "in the case of a drug product," is not required for the request for patent term extension.

(5) **A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted, 37 C.F.R. § 1.740(a)(5);**

The present application for patent term extension is being submitted within the sixty (60) day period permitted for submission pursuant to 37 C.F.R. § 1.720(f). In light of the approval on January 14, 2010, the last day for submitting the present application is March 14, 2010.

(6) **A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue and the date of expiration, 37 C.F.R. § 1.740(a)(6);**

The present application for extension is for U.S. Reissued Patent No. RE38,158, which was filed on November 4, 1998 as U.S. Reissue Application No. 09/185,732 as a reissue of U.S. Patent No. 5,583,114, which was filed on July 27, 1994 as U.S. Application No. 08/281,473 and issued on December 10, 1996.

U.S. Reissued Patent No. RE38,158 issued on June 24, 2003.

U.S. Reissued Patent No. RE38,158 expires on July 27, 2014.

The inventors of U.S. Reissued Patent No. RE38,158 are Thomas H. Barrows, Terry W. Lewis, Myhanh T. Truong, and Matthew T. Scholz.

(7) **A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings, 37 C.F.R. § 1.740(a)(7);**

A copy of U.S. Reissued Patent No. RE38,158 is attached hereto as **Exhibit B**.

(8) **A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent, 37 C.F.R. § 1.740(a)(8);**

There are no disclaimers or reexamination certificates issued on U.S. Reissued Patent No. RE38,158.

A copy of a Certificate of Correction issued by the United States Patent and Trademark Office ("U.S.P.T.O.") on April 6, 2004 for U.S. Reissued Patent No. RE38,158 is attached hereto as **Exhibit C**.

A copy of the maintenance fee payment record retrieved from the U.S.P.T.O. database relevant to U.S. Reissued Patent No. RE38,158 is attached hereto as **Exhibit D**. As indicated above, U.S. Reissued Patent No. RE38,158 was as a reissue of U.S. Patent No. 5,583,114, that issued on December 10, 1996. The first maintenance fee due was paid on March 30, 2000 against U.S. Patent No. 5,583,114. The second maintenance fee due was paid on June 10, 2004 against U.S. Reissued Patent No. RE38,158. The third maintenance fee due was paid on June 4, 2008 against U.S. Reissued Patent No. RE38,827, which was filed on November 14, 2002 as a continuation of U.S. Reissued Patent No. RE38,158 and ultimately issued on October 11, 2005. Pursuant to MPEP § 1415.01, it is respectfully submitted that the schedule of payments of maintenance fees on the original patent (i.e., U.S. Patent No. 5,583,114) will continue for the reissue patent, but such maintenance fees are no longer due in the original patent, but rather are due in the reissue patent. Additionally pursuant to MPEP § 1415.01, it is respectfully submitted that only one maintenance fee is required for all the multiple reissue patents that replaced the single original patent and the maintenance fee must be directed to the latest reissue patent that has issued.

(9) **A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent**

claim and demonstrates the manner in which at least one such patent claims reads on, 37 C.F.R. § 1.740(a)(9):

(i) The approved product, if the listed claims include any claim to the approved product;

(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product: and

(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product;

U.S. Reissued Patent No. RE38,158 claims the Neomend ProGel™ Pleural Air Leak Sealant approved on January 14, 2010. The Applicant asserts that at least claims 1, 3, 5, 6, 8, 9, 10, 15, 17-26, 28, 29, 30-35, 38, 39, 41, 43, 44, 48, 49, 113-121, 123-130, 133, 134, 136, 138, 139, 141, 144-146 and 148-150 of U.S. Reissued Patent No. RE38,158 read on the Neomend ProGel™ Pleural Air Leak Sealant, methods of making the Neomend ProGel™ Pleural Air Leak Sealant, and methods of using the Neomend ProGel™ Pleural Air Leak Sealant.

For example, claim 1 reads on the Neomend ProGel™ Pleural Air Leak Sealant as shown in Table 1, claim 17 reads on a method of making the Neomend ProGel™ Pleural Air Leak Sealant adhesive sealant as shown in Table 2, and claim 18 reads on the method of using the Neomend ProGel™ Pleural Air Leak Sealant as shown in Table 3. The cited descriptions of the Neomend ProGel™ Pleural Air Leak Sealant are available in the internal quality program document entitled Functional Testing – Surgical Sealant Kits (Document #: QP-0002 Rev. C), indicated in the tables with "A", which is attached hereto as **Exhibit E** and the FDA approved labeling, Package Insert, Document M-0005 Rev. B, indicated in the tables with "B", which is attached hereto as **Exhibit F**. Additional information is available in the document entitled Chemistry Specification (Document Number: CS-78-8110-3494-7, Revision C) indicated in the tables with "C", which is attached hereto as **Exhibit G**.

[remainder of page intentionally left blank]

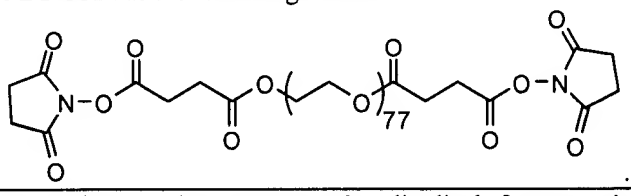
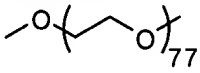
TABLE 1	
RE 38,158	**ProGEL Pleural Air Leak Sealant (hereafter "Product")**
Claim 1	
1. An adhesive composition consisting essentially of	
i) a first aqueous mixture of about 20-60 wt/vol % serum albumin	"6.2.1.4 Albumin Protein Concentration 28 – 31 gm/ 100ml" [A]
in about 0.01-0.25 molar buffer	"Preparation of Buffer Solution" yields 0.075 M (75 mM) Sodium Carbonate [C]
at a pH in a range of about 8.0-11.0,	"6.2.1.3 Albumin pH (Diluted 1:5 in 0.9% saline) 8.8 – 9.1" [A]
ii) a second aqueous mixture of about 50-800 mg/ml of a crosslinking agent	"One (1) - pre-loaded cartridge containing 260 mg of Polyethyleneglycol di-succinimidyl succinate ((PEG-(SS)2)) as a dried white powder." [B] "Step 2. Inject the 2 ml of sterile water into the cartridge containing the cross-linker, (white powder cartridge provided in the Chemistry Kit)." Thereby resulting in approximately 130mg/mL. [B]
having a molecular weight in a range of about 1,000-15,000,	"One (1) - pre-loaded cartridge containing 260 mg of Polyethyleneglycol di-succinimidyl succinate ((PEG-(SS)2)) as a dried white powder." [B] See p. 16 Molecular weight of PEG-SS2 is ~3805.
wherein the crosslinking agent is of the formula G-LM-PEG-LM-G	"One (1) - pre-loaded cartridge containing 260 mg of Polyethyleneglycol di-succinimidyl succinate ((PEG-(SS)2)) as a dried white powder." [B] PEG-SS2 has the following structure 
wherein –PEG- is a diradical fragment represented by the formula $-O-(CH_2-CH_2-O-)_a-$	According to the structure, the diradical fragment is 
wherein a is an integer from 20-300	According to the structure, a is 77

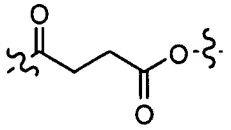
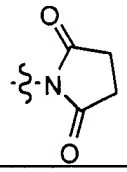
TABLE 1	
RE 38,158	**ProGEL Pleural Air Leak Sealant (hereafter "Product")**
wherein –LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula –C(O)-, a monoester diradical of the formula $-(CH_2)_bC(O)-$ where b is an integer from 1-5, a diester diradical of the formula $-C(O)-(CH_2)_c-C(O)-$ where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula $-C(O)-O-CH_2)_d-O-C(O)-$ where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, $-R-C(O)-(CH_2)_c-C(O)-$, or $-R-C(O)-O-(CH_2)_d-O-C(O)-$ where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragements selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone and p-dioxanone;	According to the structure of PEG-SS2, the diradical fragment LM is "a diester diradical of the formula –C(O)-(CH2)c-C(O)- where c is an integer from 2-10" where c is 2 having the formula: 
wherein -G is a leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl; and	According to the structure of PEG-SS2, G is succinimidyl: 

TABLE 1	
RE 38,158	**ProGEL Pleural Air Leak Sealant (hereafter "Product")**
wherein a combination of the first and second mixtures is initially liquid and then cures on the surface of tissue to give a flexible, substantive matrix which bonds to the tissue and has a burst strength greater than about 10 mmHg.	"The NeoMend Inc. ProGel™ Pleural Air Leak Sealant ("ProGel™") is a single-use medical device that is formed as a result of mixing two components: (1) a solution of human serum albumin (HSA) and (2) a synthetic cross-linking component of polyethylene glycol (PEG) that is functionalized with succinate groups. Upon mixing a clear, flexible hydrogel is formed." [B] (see 1.0 Device Description) "Step 16. Hold the spray tip approximately 5 cm (2 in) from the tissue to be sealed, and apply firm, steady pressure to the pushrod to dispense the gel to the target location. Note: As described above, the gel can be applied in either a spray pattern or a stream depending upon the amount of pressure applied to the pushrod. Applying a light pressure will cause the gel to be dispensed in a stream. Applying slightly more pressure to the pushrod will cause the stream to convert to a spray. "Step 17. Maintain firm pressure on the pushrod and move the spray tip from side to side along the margin of the tissue surface to be sealed. "Step 18. Allow the ProGel™ to cure for 15-30 seconds, forming a flexible hydrogel. Two minutes after application, the ProGel™'s success in sealing the target site(s) can be tested using the saline submersion test or by irrigating the site to check for air bubbles." [B] "6.2.4.1 Burst Pressure 90 mmHg minimum ..." [A]

[remainder of page intentionally left blank]

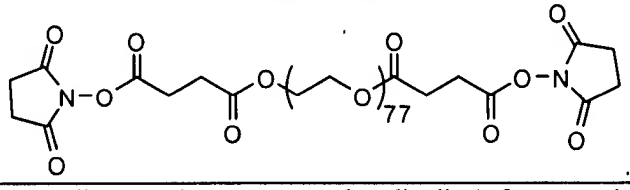
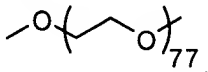
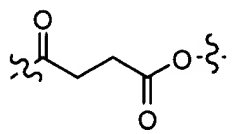
TABLE 2	
RE 38,158	**ProGEL Pleural Air Leak Sealant (hereafter "Product")**
Claim 17	
17. A method of making a tissue adhesive consisting of the step of forming a mixture of	"The NeoMend Inc. ProGel™ Pleural Air Leak Sealant ("ProGel™") is a single-use medical device that is formed as a result of mixing two components: (1) a solution of human serum albumin (HSA) and (2) a synthetic cross-linking component of polyethylene glycol (PEG) that is functionalized with succinate groups. Upon mixing a clear, flexible hydrogel is formed." [B] (see 1.0 Device Description)
i) a first aqueous mixture of about 20-60 wt/vol % serum albumin	"6.2.1.4 Albumin Protein Concentration 28 – 31 gm/ 100ml"[A]
in about 0.01-0.25 molar buffer	"Preparation of Buffer Solution" yields 0.075 M (75 mM) Sodium Carbonate [C]
at a pH in a range of about 8.0-11.0,	"6.2.1.3 Albumin pH (Diluted 1:5 in 0.9% saline) 8.8 - 9.1"[A]
ii) a second aqueous mixture of about 50-800 mg/ml of a crosslinking agent	"One (1) - pre-loaded cartridge containing 260 mg of Polyethyleneglycol di-succinimidyl succinate ((PEG-(SS)2)) as a dried white powder." [B] "Step 2. Inject the 2 ml of sterile water into the cartridge containing the cross-linker, (white powder cartridge provided in the Chemistry Kit)." Thereby resulting in approximately 130mg/mL. [B]
having a molecular weight in a range of about 1,000-15,000,	"One (1) - pre-loaded cartridge containing 260 mg of Polyethyleneglycol di-succinimidyl succinate ((PEG-(SS)2)) as a dried white powder." [B] See p. 16 Molecular weight of PEG-SS2 is ~3805.
wherein the crosslinking agent is of formula G-LM-PEG-LM-G	"One (1) - pre-loaded cartridge containing 260 mg of Polyethyleneglycol di-succinimidyl succinate ((PEG-(SS)2)) as a dried white powder." [B] PEG-SS2 has the following structure 
wherein –PEG– is a diradical fragment represented by the formula -O-(CH_2-CH_2-O-)$_a$-	According to the structure, the diradical fragment is 
where a is an integer from 20-300;	According to the structure, a is 77
wherein –LM– is a diradical fragment selected from the group consisting of a carbonate diradical of the formula –C(O)-, a monoester diradical of the formula –(CH_2)$_b$C(O)– where b is an integer from 1-5, a diester diradical of the formula –C(O)-(CH_2)$_c$-C(O)– where c is an integer from 2-10 and where the aliphatic portion of the	According to the structure of PEG-SS2, the diradical fragment LM is "a diester diradical of the formula –C(O)-(CH2)c-C(O)- where c is an integer form 2-10" where c is 2 having the formula: 

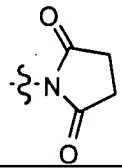
TABLE 2	
RE 38,158	**ProGEL Pleural Air Leak Sealant (hereafter "Product")**
diradical may be saturated or unsaturated, a dicarbonate diradical of the formula $-C(O)-O-CH_2)_d-O-C(O)-$ where d is an integer from 2-10, and an oligomeric diradical represented by the formulas -R-C(O)-, $-R-C(O)-(CH_2)_c-C(O)-$, or $-R-C(O)-O-(CH_2)_d-O-C(O)-$ where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragements selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone or p-dioxanone;	
wherein -G is a leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl; and	According to the structure of PEG-SS2, G is succinimidyl: 
wherein the combination of the first and second mixtures is initially liquid and then cures on the surface of tissue to give a flexible, substantive matrix which bonds to the tissue and has a burst strength greater than about 10 mmHg.	"The NeoMend Inc. ProGel™ Pleural Air Leak Sealant ("ProGel™") is a single-use medical device that is formed as a result of mixing two components: (1) a solution of human serum albumin (HSA) and (2) a synthetic cross-linking component of polyethylene glycol (PEG) that is functionalized with succinate groups. Upon mixing a clear, flexible hydrogel is formed." [B] (see 1.0 Device Description) "Step 16. Hold the spray tip approximately 5 cm (2 in) from the tissue to be sealed, and apply firm, steady pressure to the pushrod to dispense the gel to the target location. Note: As described above, the gel can be applied in either a spray pattern or a stream depending upon the amount of pressure applied to the pushrod. Applying a light pressure will cause the gel to be dispensed in a stream. Applying slightly more pressure to the pushrod will cause the stream to convert to a spray. "Step 17. Maintain firm pressure on the pushrod and move the spray tip from side to side along the margin of the tissue surface to be sealed. "Step 18. Allow the ProGel™ to cure for 15-30 seconds, forming a flexible hydrogel. Two minutes after application, the ProGel™'s success in sealing the target site(s) can be tested using the saline submersion test or by irrigating the site to check for air bubbles." [B] "6.2.4.1 Burst Pressure 90 mmHg minimum ..." [A]

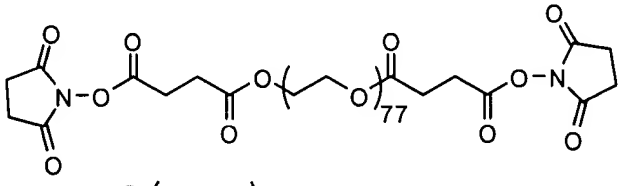
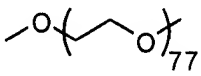
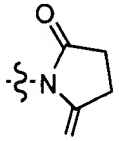
TABLE 3	
RE 38,158	**ProGEL Pleural Air Leak Sealant (hereafter "Product")**
Claim 18	
18. A method of treating tissue to prevent or control air or fluid leaks comprising:	Product Name: "ProGel Pleural Air Leak Sealant"
providing a composition to tissue,	". . . intended for application to visceral pleura . . ." [B] "Step 17. Maintain firm pressure on the pushrod and move the spray tip from side to side along the margin of the tissue surface to be sealed." [B] See steps 14-18.
said composition including a serum albumin protein at about 20-60 wt/vol % and	"6.2.1.4 Albumin Protein Concentration 28 – 31 gm/ 100ml"[A]
a crosslinking agent at about 50-800 mg/ml,	"One (1) - pre-loaded cartridge containing 260 mg of Polyethyleneglycol di-succinimidyl succinate ((PEG-(SS)2)) as a dried white powder." [B] See p. 16 "Step 2. Inject the 2 ml of sterile water into the cartridge containing the cross-linker, (white powder cartridge provided in the Chemistry Kit)." Thereby resulting in approximately 130mg/mL. [B]
said crosslinking agent having a polyoxyethylene chain portion and an activated leaving group which allows the crosslinking agent to react with said protein and	"One (1) - pre-loaded cartridge containing 260 mg of Polyethyleneglycol di-succinimidyl succinate ((PEG-(SS)2)) as a dried white powder." [B] See p. 16 PEG-SS2 has the structure:  Where  is "polyoxyethylene chain"  and O is an activated leaving group. Crosslinking occurs by exchanging succinimidyl group for accessible amine of protein.
having a molecular weight in a range of about 1,000-15,000; and	PEG-SS2 has an estimated molecular weight of ~3805.

TABLE 3	
RE 38,158	**ProGEL Pleural Air Leak Sealant (hereafter "Product")**
curing said composition on the tissue to bond said composition to the tissue and to provide a substantive cured matrix that has a burst strength greater than about 10 mm Hg.	"The NeoMend Inc. ProGel™ Pleural Air Leak Sealant ("ProGel™") is a single-use medical device that is formed as a result of mixing two components: (1) a solution of human serum albumin (HSA) and (2) a synthetic cross-linking component of polyethylene glycol (PEG) that is functionalized with succinate groups. Upon mixing a clear, flexible hydrogel is formed." [B] (see 1.0 Device Description) "Step 16. Hold the spray tip approximately 5 cm (2 in) from the tissue to be sealed, . . . the gel can be applied in either a spray pattern or a stream . . . "Step 17. Maintain firm pressure on the pushrod and move the spray tip from side to side along the margin of the tissue surface to be sealed. "Step 18. Allow the ProGel™ to cure for 15-30 seconds, forming a flexible hydrogel. Two minutes after application, the ProGel™'s success in sealing the target site(s) can be tested using the saline submersion test or by irrigating the site to check for air bubbles." [B] "6.2.4.1 Burst Pressure 90 mmHg minimum ..." [A]

[remainder of page intentionally left blank]

(10) **A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services or Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period, as follows, 37 C.F.R. § 1.740(a)(10):**

(v) For a patent claiming a medical device:

A. **The effective date of the investigational device exemption (IDE) and the IDE number, if applicable, or the date on which the applicant began the first clinical investigation involving the device, if no IDE was submitted, and any available substantiation of that date;**

The effective date of the investigational device exemption ("IDE") is June 29, 1999. The IDE number was G980283 3M Polymeric Patch. A copy of the IDE conditional approval letter from the FDA dated June 29, 1999 is attached hereto as **Exhibit H**.

B. **The date on which the application for product approval or notice of completion of product development protocol under Section 515 of the Federal Food, Drug and Cosmetic Act was initially submitted and the number of the application; and**

The application for product approval under Section 515 of the Federal Food, Drug, and Cosmetic Act, i.e., the Premarket Approval Application (PMA) was submitted on August 22, 2001 and was accepted by the FDA on August 23, 2001. The PMA number was P010047. A copy of the PMA acceptance letter from the FDA dated August 23, 2001 is attached hereto as **Exhibit I.**

C. **The date on which the application was approved or the protocol declared to be completed.**

The PMA was approved on January 14, 2010. See **Exhibit A** referenced above.

(11) **A brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities, 37 C.F.R. § 1.740(a)(11).**

A table listing the significant activities undertaken by the marketing Applicant, or its predecessor(s), during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities is attached hereto as **Exhibit J.**

The marketing Applicant is Neomend, Inc. Neomend, Inc. acquired ownership rights in the 3M Surgical Sealant, including PMA No. P010047, which is now the approved product, Neomend ProGel™ Pleural Air Leak Sealant, from 3M Company and 3M Innovative Properties Company on June 22, 2007 pursuant to an Asset Purchase and License Agreement dated June 5, 2007. Accordingly, all regulatory activities relating to the approved product, Neomend ProGel™ Pleural Air Leak Sealant, prior to the closing date of June 22, 2007 were undertaken by 3M Company and/or 3M Innovative Properties Company and all regulatory activities relating to the approved product, Neomend ProGel™ Pleural Air Leak Sealant, beginning on June 22, 2007 and thereafter were undertaken by Neomend. A copy of Neomend's letter to the FDA dated June 25, 2007 notifying the FDA of the transfer of ownership of PMS No. P010047 from 3M to Neomend is attached hereto as **Exhibit K**. A copy of the FDA's letter acknowledging the change is ownership dated June 27, 2007 is attached hereto as **Exhibit L**.

[remainder of page intentionally left blank]

(12) **Statement that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined, 37 C.F.R. § 1.740(a)(12);**

(A) Eligibility. The Applicant respectfully submits that U.S. Reissued Patent No. RE38,158 is eligible for extension under 35 U.S.C. § 156 as set forth below:

(1) 35 U.S.C. § 156(a)

As set forth in Section (9) above, Applicant submits that one or more of the claims of U.S. Reissued Patent No. RE38,158 claim the approved product, Neomend ProGel™ Pleural Air Leak Sealant.

(2) 35 U.S.C. § 156(a)(1)

U.S. Reissued Patent No. RE38,158 is granted and has not expired before the submission of this application and there are no terminal disclaimers.

(3) 35 U.S.C. § 156(a)(2)

The term of U.S. Reissued Patent No. RE38,158 has not, to Neomend Inc.'s knowledge, been extended before the submission of this instant application.

(4) 35 U.S.C. § 156(a)(3)

This application is being submitted by Neomend, Inc. as the owner of record of U.S. Reissued Patent No. RE38,158.

The inventors Thomas H. Barrows, Terry W. Lewis and Mynanh T. Truong assigned their entire right, title and interest in the invention entitled "Adhesive Sealant Composition," which was assigned U.S. Application No. 08/281,473 and which issued as U.S. Patent No. 5,583,114, to Minnesota Mining and Manufacturing Company on July 27, 1994, which was recorded with the U.S.P.T.O. on July 27, 1994 at Reel 007123, Frame 0460. See **Exhibit M**. The inventor Matthew T. Scholz assigned his entire right, title and interest in the invention entitled "Adhesive Sealant Composition" filed July 27, 1994, which was assigned U.S. Application No. 08/281,473 and issued as U.S. Patent No. 5,583,114 to Minnesota Mining and Manufacturing Company on October 2, 1998, which was recorded with the U.S.P.T.O. on November 4, 1998 at Reel 009564, Frames 0154-0155. See **Exhibit N**. 3M Company (Formerly Minnesota Mining and Manufacturing Company), a corporation of the State of Delaware, assigned its entire right, titled and interest in Reissued Patent No. RE38,158 to 3M Innovative Properties Company on September 9, 2004, which was recorded with the U.S.P.T.O. on

September 10, 2004 at Reel 015116, Frames 0336-0337. See **Exhibit O**. 3M Innovative Properties Company assigned its entire right, titled and interest in Reissued Patent No. RE38,158 to Neomend, Inc. on June 21, 2007, which was recorded with the U.S.P.T.O. on August 20, 2009 at Reel 023119, Frames 0699-0704. See **Exhibit P**.

(5) 35 U.S.C. § 156(a)(4)

As evidenced by the January 14, 2010 approval letter from the FDA (see **Exhibit A** referenced above), Neomend ProGel™ Pleural Air Leak Sealant was subjected to the regulatory review period pursuant under Section 515 of the Federal Food, Drug, and Cosmetic Act, before its commercial marketing or use.

(6) 35 U.S.C. § 156(a)(5)(A)

The permission for commercial marketing of Neomend ProGel™ Pleural Air Leak Sealant is the first permitted commercial marketing of Neomend ProGel™ Pleural Air Leak Sealant under the provisions of the FDCA (21 U.S.C. § 515) under which the regulatory review period occurred, as confirmed by the absence of any approved PMA for the approved product prior to January 14, 2010.

(7) 35 U.S.C. § 156(c)(4)

No other patent has been extended for the same regulatory review period for the product Neomend ProGel™ Pleural Air Leak Sealant.

(8) This application otherwise complies with all the requirements of 35 U.S.C. § 156 and the applicable rules and procedures.

(B) Calculation of extension period. The period which the term of U.S. Reissued Patent No. RE38,158 is requested by the Applicant to be extended is one thousand eight hundred and twenty-six (1826) days (i.e., five (5) years) from July 27, 2014, such that U.S. Reissued Patent No. RE38,158 would expire on July 27, 2019:

The number of days in the IDE testing period of paragraph(c)(1) extends from the effective date of IDE No. G980283 on June 29, 1999 to the conclusion of the IDE testing period on October 11, 2001, which is eight hundred thirty-six (836) days. The IDE testing period concluded upon 3M's submission of the IDE Final Report to the FDA on October 11, 2001. A copy of the cover letter that enclosed a copy of 3M's IDE Final Report to the FDA dated October 11, 2001 is attached hereto as **Exhibit Q**.

The number of days in the PMA approval review period of paragraph (c)(2) extends from the filing of the PMA No. P010047 on August 23, 2001 (see **Exhibit I** referenced above) to the date of approval of the PMA on January 14, 2010, which is three thousand sixty-seven (3067) days. A first Directed Hold Request was submitted by 3M on April 19, 2004, which is attached hereto as **Exhibit R**. A copy of the FDA's letter accepting the first Directed Hold dated April 20, 2004, at which time the approval period was on hold, is attached hereto as **Exhibit S.** The first Directed Hold was requested to be removed by Neomend on June 25, 2007, (see **Exhibit K** referenced above). A copy of the FDA's letter accepting the removal of the first Directed Hold to NeoMend dated June 27, 2007, at which time the approval period was re-initiated (see **Exhibit L** referenced above). A second Directed Hold was submitted by Neomend, Inc. on October 4, 2007, which is attached hereto as **Exhibit T.** A copy of the FDA's letter accepting the second Directed Hold dated October 10, 2007, at which time the approval period was on hold, is attached hereto as **Exhibit U.** The second Directed Hold was requested to be removed by Neomend on November 1, 2007, which is attached hereto as **Exhibit V**. A copy of the FDA's letter accepting the removal of the second Directed Hold to Neomend dated November 2, 2007, at which time the approval period was re-initiated, is attached hereto as **Exhibit W.** The total number of days the PMA was subject to a Directed Hold was one thousand one hundred eighty-six (1186) days, which is equal to one thousand one hundred sixty-three (1163) days for the first Directed Hold timed period plus twenty-three (23) days for the second Directed Hold time period. Accordingly, Applicant hereby submits that the approval period of three thousand sixty-seven (3067) days should be shortened by the one thousand one hundred eighty-six (1186) days the PMA was subject to two Directed Hold periods, and therefore submits that the approval period is one thousand eight hundred eighty-one (1881) days.

Summary:

Period of Extension	= ½ (Testing Period)	+ Approval Period
	= ½ (836 days)	+ 1881 days
	= 2299 days	

The Applicant respectfully requests an extension of five (5) years based on the above calculations, whose total exceeds five (5) years. Applicant respectfully submits that the term of the patent after the date of approval of the approved product when added to the requested five (5) year extension does not exceed fourteen (14) years.

Applicant respectfully submits that U.S. Reissued Patent No. RE38,158 should be extended to July 27, 2019.

[remainder of page intentionally left blank]

(13) **Statement that the applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought, 37 C.F.R. § 1.740(a)(13).**

The Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) **The prescribed fee for receiving and acting upon the application for extension, 37 C.F.R. § 1.740(a)(14).**

Pursuant to 37 C.F.R. § 1.20(j) a check for the application fee in the amount of $1,120.00 is enclosed with this application.

Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of the same, the Director is hereby authorized to charge Deposit Account No. 50-0436 for any such fees. Should a refund of fee paid be necessary, the Director is hereby authorized to credit any such amount to Deposit Account No. 50-0436.

[remainder of page intentionally left blank]

(15) **The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed, 37 C.F.R. § 1.740(a)(15).**

Please direct all inquires, questions and correspondence regarding this application to the undersigned.

Respectfully submitted,

N. Nicole Endejann, Reg. No. 50,229 and
Raymond A. Miller, Reg. No. 42,891

PEPPER HAMILTON LLP
One Mellon Center, 50th Floor
500 Grant Street
Pittsburgh, PA 15219
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E-Mail: millerra@pepperlaw.com
Date: March 2, 2010

EXHIBIT A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
9200 Corporate Blvd
Rockville, MD 20850

JAN 14 2010

NeoMend, Inc
% Mr. Jeffrey A. Anderson
Vice President, Regulatory and
Clinical Affairs
60 Technology Drive
Irvine, California 92618

Re: P010047
ProGel™ Pleural Air Leak Sealant
Filed: August 23, 2001
Amended: March 26, April 5, September 27, October 28, 2002 and March 14 and December 4, 2003, and March 31 and April 20, 2004, June 27, October 10, and November 2, 2007 and January 23, March 10, July 15 and 30, August 20, October 10, November 13 and 26, 2008 and February 5, September 17, October 1 and 30, 2009
Procode: NBE

Dear Mr. Anderson:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for ProGel™ Pleural Air Leak Sealant. This device is indicated for application to visceral pleura during an open thoracotomy after standard visceral pleural closure with, for example, sutures or staples, of visible air leaks (≥ 2 mm) incurred during open resection of lung parenchyma. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). FDA has determined that this restriction on sale and distribution is necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Expiration dating for this device has been established and approved at 12 months.

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The

Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the Annual Report requirements, you have agreed to provide the following data in post-approval study reports (PAS). Two copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below.

The objective of the Post Approval Study (PAS) is to evaluate the long-term safety of the device. The PAS will be a non-randomized, sequential-enrollment controlled, multi-center 90-day follow-up trial on 400 subjects (i.e., 267 device and 133 control patients) from the pivotal study centers and up to 20 other expert centers. Study subjects will be consecutively enrolled in two sequential non-overlapping phases under a common protocol at each center, first into the control group and then into the device group. All subjects will be followed for 90 days. The control subjects will receive current standard of care for an air leak following pulmonary surgery. The proposed study is a safety study with twelve adverse events of interest:

1. Pulmonary:
    a. Pneumothorax
    b. Air leak, persistent
    c. Air leak, late onset
    d. Residual pleural space
    e. ARDS

2. Post-surgical renal abnormalities

3. Cardiovascular
    a. Myocardial infarction
    b. Atrial arrhythmia
    c. Ventricular arrhythmia
    d. Cardiac arrest

4. Death (all-cause)

5. Hospital readmission

Summary descriptive statistics will be reported for all baseline and demographic parameters and each outcome endpoint will be evaluated by the differences in proportions of cases compared to controls with upper one-sided 95% confidence bounds. Event rates for power calculations were estimated based on prior IDE studies or published literature. Sample size calculations used a non-inferiority model with one-sided significance of .05 and statistical power of 80%.

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA.

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a complete protocol of your post-approval study. Your PMA supplement should be clearly labeled as a "Post-Approval Study Protocol" and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm#2).

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction

were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing. One of those three copies may be an electronic copy (eCopy), in an electronic format that FDA can process, review and archive (general information.

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.htm; clinical and statistical data: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm136377.htm)

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Charles N. Durfor, Ph.D. (301) 796-6970.

Sincerely yours,

Mark N. Melkerson
Director
Division of Surgical, Orthopedic
and Restorative Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

EXHIBIT B

US00RE38158E

(19) **United States**
(12) **Reissued Patent**
Barrows et al.

(10) **Patent Number: US RE38,158 E**
(45) **Date of Reissued Patent: Jun. 24, 2003**

(54) **ADHESIVE SEALANT COMPOSITION**

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(73) Assignee: **Minnesota Mining and Manufacturing Company**, St. Paul, MN (US)

(21) Appl. No.: **09/185,732**

(22) Filed: **Nov. 4, 1998**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **5,583,114**
Issued: **Dec. 10, 1996**
Appl. No.: **08/281,473**
Filed: **Jul. 27, 1994**

(51) **Int. Cl.**[7] **A61K 38/00**; A61K 39/00; C07K 1/00

(52) **U.S. Cl.** **514/21**; 424/179.1; 424/193.1; 424/194.1; 424/422; 424/423; 424/428; 424/77; 424/78.02; 424/78.06; 514/2; 514/4; 525/54.1; 530/362; 530/363; 530/366; 530/830

(58) **Field of Search** 514/2, 4, 21; 530/350, 530/362, 363, 366, 830, 364, 365, 367, 368, 369, 409, 410; 424/77, 78.02, 78.06, 422, 423, 428, 179.1, 193.1, 194.1, 78.17, 426, 484, 486; 525/54.1; 602/54, 55, 56, 57; 106/33, 124.3, 124.5, 155.21, 156.2, 156.5, 158.1

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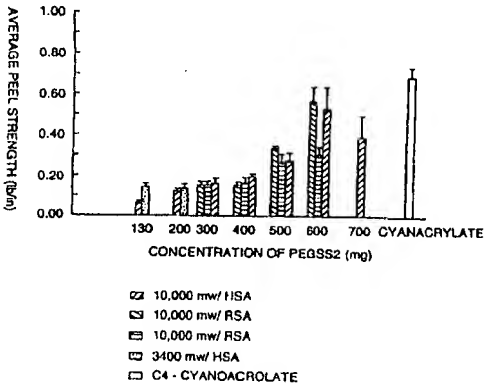
Primary Examiner—Jeffrey E. Russel
(74) *Attorney, Agent, or Firm*—Fish & Richardson P.C.

(57) **ABSTRACT**

This invention is related to an adhesive composition which may be used to bond or seal tissue in vivo. The adhesive composition is readily formed from a two component mixture which includes a first part of a protein, preferably a serum albumin protein, in an aqueous buffer having a pH in the range of about 8.0–11.0 and a second part of a water-compatible or water-soluble bifunctional crosslinking agent. When the two parts of the mixture are combined, the mixture is initially a liquid which cures in vivo on the surface of tissue in less than about one minute to give a strong, flexible, pliant substantive composition which bonds to the tissue and is absorbed in about four to sixty days. The adhesive composition may be used either to bond tissue, to seal tissue or to prevent tissue adhesions caused by surgery.

154 Claims, 3 Drawing Sheets



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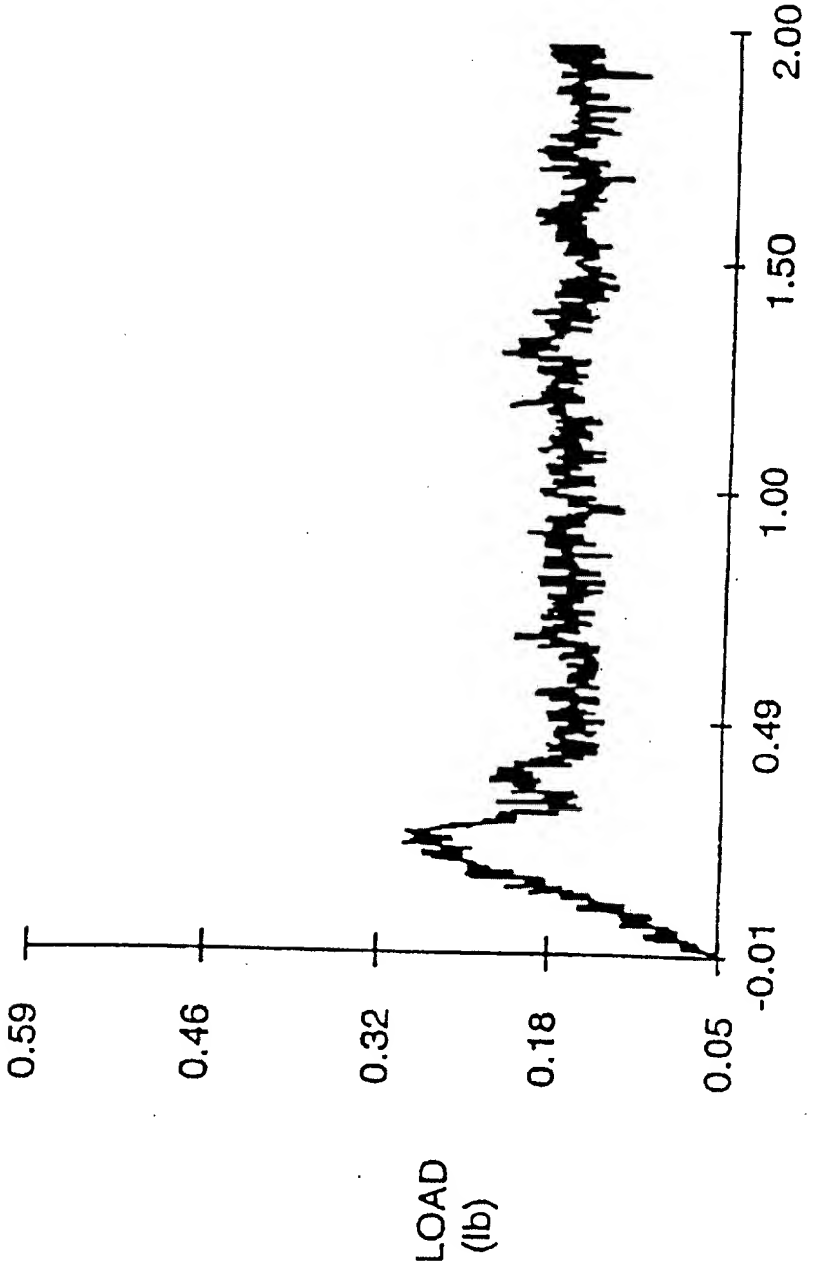
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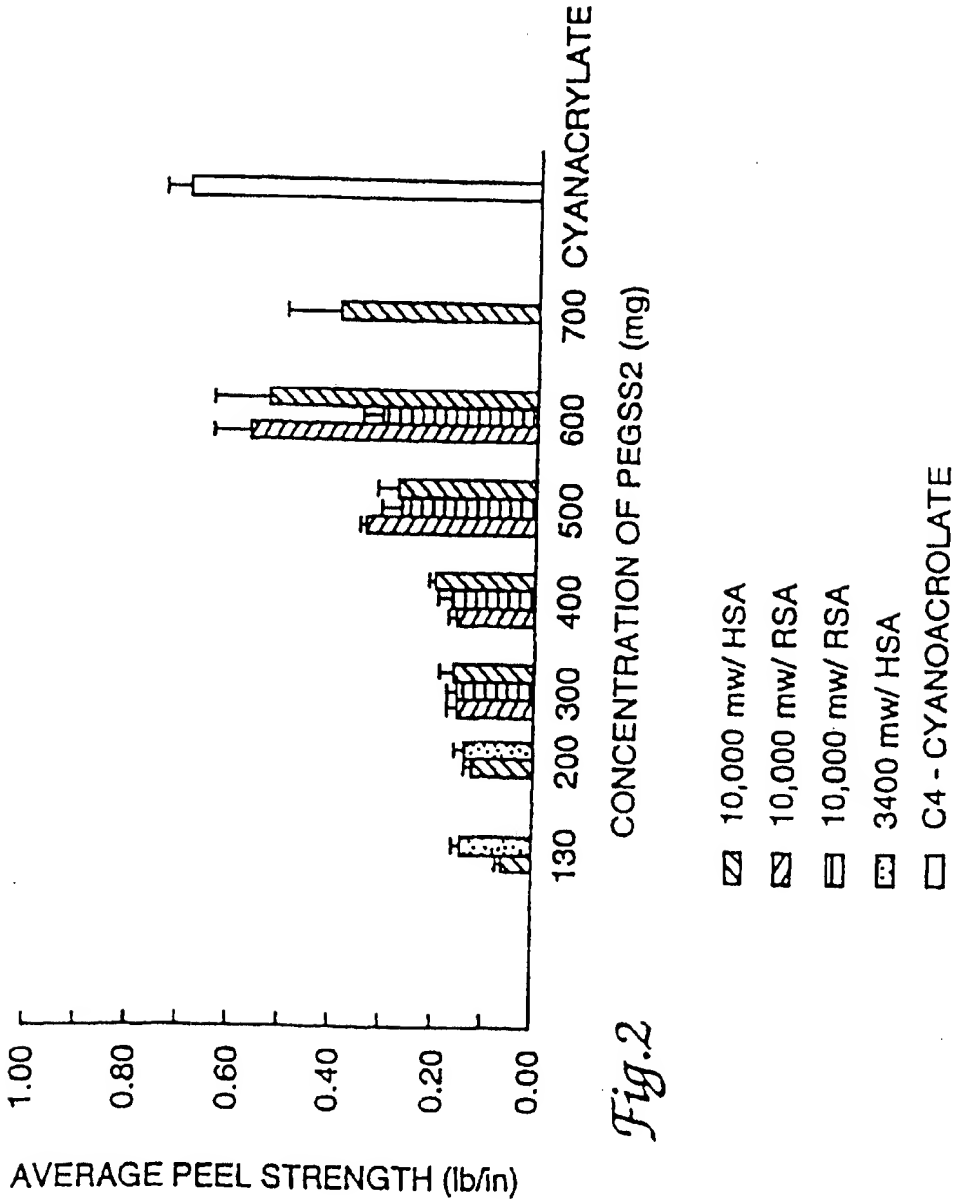
2.00
DISPLACEMENT (in)

Fig.1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0.60
0.40
0.20
0.00
130
200
300
400
500
600
700
CYANACRYLATE
CONCENTRATION OF PEGSS2 (mg)
10,000 mw/ HSA
10,000 mw/ RSA
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3400 mw/ HSA
C4 - CYANOACROLATE

Fig.2

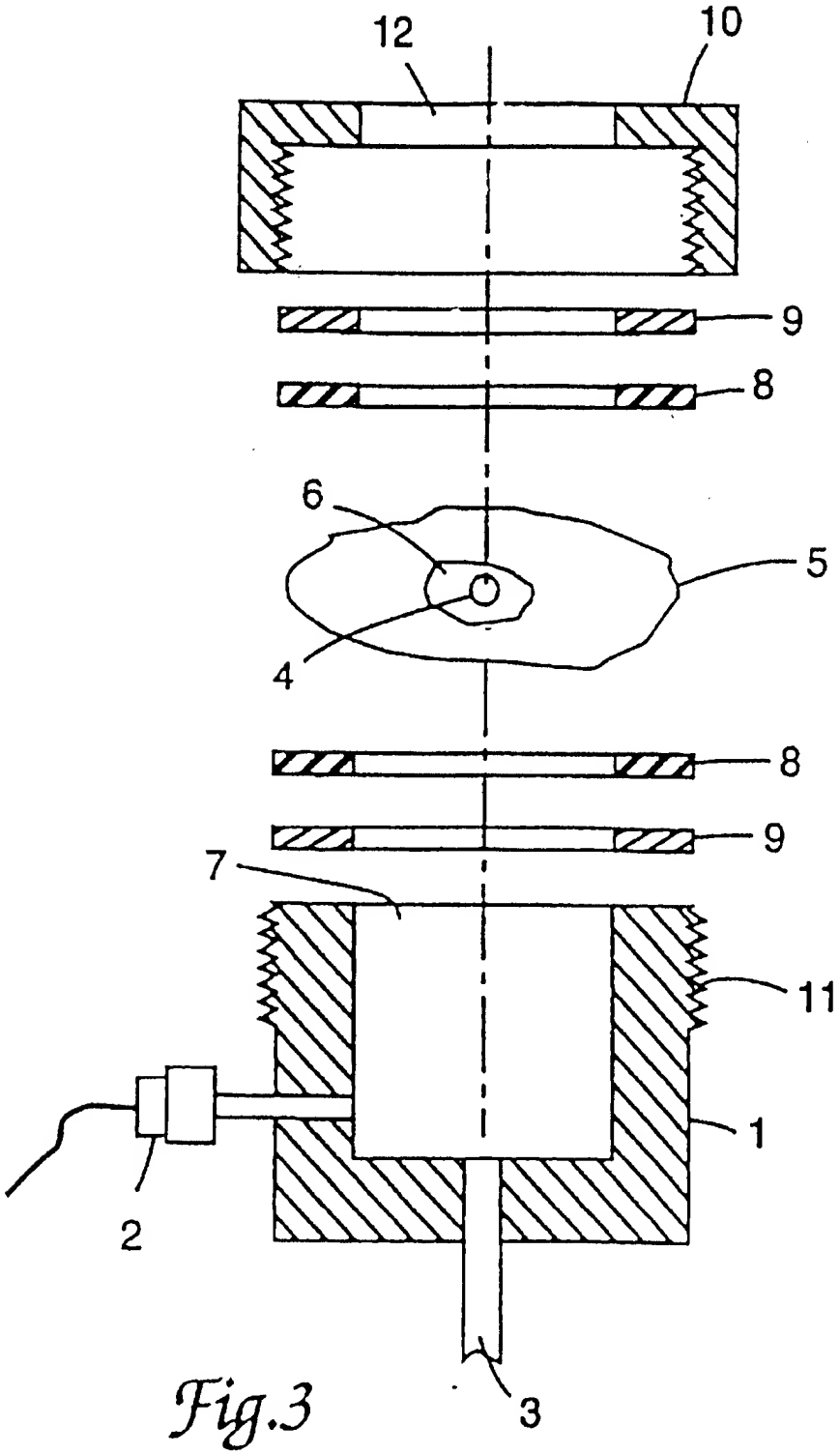


Fig.3

ADHESIVE SEALANT COMPOSITION

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

Notice: More than one reissue appliation has been filed for the reissue of U.S. Pat. No. 5,583,114. The reissue applications are application Ser. Nos. 09/185,732 (the present application), and 10/293,989, filed Nov. 14, 2002, all of which are reissues of U.S. Pat. No. 5,583,114.

The present invention is generally related to an adhesive sealant composition which may be used to bond or seal tissue in vivo and is particularly related to a two component, liquid adhesive composition which is mixed together as it is applied to tissue and then cured in vivo in order to bond tissue, to seal tissue to prevent or control pulmonary system air leaks, or to prevent tissue adhesions caused by surgery.

BACKGROUND

A variety of techniques have been used to bond or seal tissue. For example, different types of tissues have been mechanically bound or sealed with a number of procedures, materials and methods including sutures, staples, tapes and bandages. In some applications, these materials are made of absorbable materials which are intended to bond and/or seal tissue as it heals and then to be absorbed over a period of time.

The common use of a medical adhesive or "tissue glue" has not found widespread application. To date, some adhesive materials are known which may be used to adhere or stick tissue such as skin. For example, cyanoacrylate adhesives such as HISTOACRYL adhesive available from B. Braun, Melsungen, Germany or VETBOND tissue adhesive available from 3M, St. Paul, Minn. may be used to bond tissue. In addition to cyanoacrylate adhesives, other types of materials have been reported to adhere to stick to skin. For example, U.S. Pat. No. 4,839,345 to Doi et al. reports a hydrated crosslinked protein adhesive gel that is used as a cataplasm or cosmetic mask that will externally adhere to skin but can be easily removed or pulled off and then readhered to the skin. Other crosslinked protein hydrogels have been reported to serve as a proteinaceous substrate to deliver therapeutic agents such as enzymes or drugs through skin or mucous membranes. See, for example, International Patent Application Ser. No. PCT/US93/07314 filed Aug. 4, 1993. Still other materials have been used as hemostatic agents to stop or prevent bleeding. In particular, mixtures of fibrinogen and thrombin such as TISSEEL sealant available from Immuno AG, Vienna, Austria or BERIPLAST-P hemostatic agent or sealant available from Behringwerke, Marburg, Germany, have been used in vascular surgery to seal tissue such as blood vessels and thus prevent blood leakage.

In sum, there are few available adhesive compositions that have sufficient strength, biocompatibility and bioabsorbability as well as other desired properties that would allow such compositions to be readily used in current medical procedures or practices. The unavailability of a suitable tissue adhesive or sealant may be related to the stringent requirements that a suitable, useful tissue adhesive must meet. Importantly, a tissue adhesive must provide substantial bonding strength for either internal or external tissues. The adhesive should be made of a biocompatible material which does not interfere with normal healing or regeneration processes. A suitable tissue adhesive must also

be easily administered in a liquid form and then rapidly cured, ideally in less than a minute, once applied. In addition, a tissue adhesive must remain flexible, pliant and have good mechanical strength after being cured. Finally, a tissue adhesive must be completely absorbed or broken down in vivo, without producing an allergic response, adverse tissue reaction or systemic toxic effects, in an acceptable time period. Preferably a suitable adhesive would also be readily absorbed after it is applied.

SUMMARY OF THE INVENTION

The present invention is a nontoxic, absorbable adhesive sealant composition which may be used to bond and/or seal tissue. The adhesive composition is readily formed from a two component mixture which includes a first part of a protein, preferably a serum protein such as albumin, in an aqueous buffer having a pH in the range of about 8.0–11.0 and a second part of a water-compatible or water-soluble bifunctional crosslinking agent. When the two parts of the mixture are combined, the mixture is initially liquid. The combined mixture then cures in vivo on the surface of tissue in less than about one minute to give a strong, flexible, pliant substantive composition which securely bonds to the tissue and is readily absorbed in about four to sixty days, preferably in about four to twenty-eight days.

In a preferred embodiment of the invention, an adhesive sealant composition is formed from a two part mixture that includes a proportion of a volume of a buffered basic serum albumin protein solution to a volume of a polyethylene glycol disuccinimidoyl succinate crosslinking agent in a range of from about 1:10 parts albumin solution by volume to about 10:1 parts by volume crosslinking agent. In order to facilitate the mixing of the two parts of the present adhesive composition, the volume to volume ratio of albumin solution to crosslinking agent is preferably a ratio of 1:1.

Preferred serum albumin proteins are selected to prevent adverse tissue or unwanted immunological responses. When the present adhesive mixture is used to bond or seal human tissue, a preferred serum albumin is purified human serum albumin which has been sterilized, dialyzed with a basic buffer having a pH value of about 8.0–11.0, concentrated by ultrafiltration through a membrane having about a 50,000 molecular weight cut-off to yield a concentrated, buffered aqueous mixture having about 20–60 wt/vol %, preferably about 35–45 wt/vol %, human serum albumin.

Preferred bifunctional crosslinking agents include polyethylene glycol derived crosslinking agents having a molecular weight (weight average) in a range of about 1,000–15,000 and preferably in a range of about 2,006–4,000. When the molecular weight of the crosslinking agent is in the range of about 1,000–5,000 the crosslinking agent is generally dissolved in water at a concentration of about 50–300 mg/ml. Similarly, when the molecular weight of the crosslinking agent is in the range of about 5,000–15,000 the crosslinking agent is generally dissolved in water at a concentration in the range of about 300–800 mg/ml.

The adhesive composition of this invention may be used in a variety of applications. Some applications include using the adhesive sealant composition to bind tissue together either as an adjunct to or as a replacement of sutures, staples, tapes and/or bandages. In another application, the present adhesive may be used to prevent post-surgical adhesions. In this application, the adhesive composition is applied and cured as a layer on surfaces of internal organs or tissues in order to prevent the formation of adhesions at a surgical site as the site heals. Additional applications include sealing

tissues to prevent or control blood or other fluid leaks at suture or staple lines as well as to prevent or control air leaks in the pulmonary system.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graphical representation of a measured peel force of an adhesive composition of this invention.

FIG. 2 is a graphical representation of peel force measurements of different adhesive composition samples which are used to adhere excised guinea pig skin strips together.

FIG. 3 is a schematic diagram of an apparatus used to measure burst strength of an adhesive sealant composition.

DETAILED DESCRIPTION

The present invention is related to an adhesive composition which has high mechanical strength, flexibility, fast cure rate and sufficient adhesion needed to bond and/or seal tissue in vivo. The adhesive composition is made of two components, a buffered basic protein solution and a bifunctional crosslinking agent. The buffered protein solution and the bifunctional crosslinking agent are typically prepared using commercially available materials and established synthetic methods. The use of known, commercially available materials in the preparation of the adhesive composition provides a benefit in the practice of this invention because most of these materials generally have a history of clinical safety and/or use.

Suitable proteins for use in the present adhesive composition include nonimmunogenic, water soluble proteins. Serum lipoproteins are particularly well suited for this purpose because these proteins bind to lipids and also exhibit a relatively high elasticity in the natured or seminatured state. These properties are believed to provide a cured matrix which is strong as well as pliant and elastic. Other soluble proteins, in addition to serum lipoproteins, are also suitable for use in the present invention. Aqueous mixtures of proteins such as derivatives of elastin, fibrinogen and collagen may be used in the present invention.

Preferred buffered protein solutions which may be used in the present adhesive composition include concentrated aqueous serum albumin protein mixtures that are buffered to a pH of between about 8.0–11.0 where the buffer concentration is in a range of about 0.01–0.25 molar. Suitable buffer systems include buffers which are physiologically and/or clinically acceptable such as known carbonate or phosphate buffer systems, provided the buffer does not adversely react with or otherwise alter the crosslinking agent. A preferred buffer system is a carbonate/bicarbonate buffer system at a pH value of about 9.0–10.5 at a concentration in the range of 0.05–0.15 molar.

Serum albumin protein is readily isolated from serum using known isolation processes. In addition, it is possible to produce human serum albumin from genetically transformed cells. See, for example, the reports of Quirk et al., *Biotechnology and Applied Biochemistry,* 11:273–287 (1989), Kalman et al., *Nucleic Acids Research,* 18:6075–6081 (1990), Sleep et al., *Biotechnology,* 8:42–46 (1990), and Sijmons et al., *Biotechnology,* 8:217–221 (1990). The ability to produce human serum albumin recombinantly provides the benefit that protein produced by this method will be free of pathogens, viruses or other contaminants that might contaminate albumin that is isolated directly from serum.

When used in the present buffered mixtures it has been found that the serum albumin is not denatured. Because the albumin is not denatured before it is used it is believed that the albumin proteins retain their natured, coiled conformation and thus, after being crosslinked during the curing process to provide a gel-like solid, the cured adhesive retains sufficient flexibility to provide a suitable adhesive matrix.

A variety of suitable crosslinking agents may be used in the present invention. Preferred crosslinking agents include a polyethylene glycol or polyoxyethylene chain portion (—PEG—), an activated leaving group portion (—G) and a linking moiety (—LM—) which binds the —PEG— portion and the leaving group portion —G. Crosslinking agents include compounds of the formula

G—LM—PEG—LM—G

in which —PEG— is a diradical fragment represented by the formula

$$—O—(CH_2—CH_2—O—)_a—$$

where a is an integer from 20–300; —LM— is also a diradical fragment such as a carbonate diradical represented by the formula, —C(O)—, a monoester diradical represented by the formula, $—(CH_2)_bC(O)—$ where b is an integer from 1–5, a diester diradical represented by the formula, $—C(O)—(CH_2)_c—C(O)—$ where c is an integer from 2–10 and where the aliphatic portion of the radical may be saturated or unsaturated, a dicarbonate represented by the formula $—C(O)—O—(CH_2)_d—O—C(O)—$ where d is an integer from 2–10, or an oligomeric diradical represented by the formulas —R—C(O)—, $—R—C(O)—(CH_2)_c—C(O)—$, or $—R—C(O)—O—(CH_2)_d—O—C(O)—$ where c is an integer from 2–10, d is an integer from 2–10, and R is a polymer or copolymer having 1–10 monomeric lactide, glycolide, trimethylene carbonate, caprolactone or p-dioxanone fragments; and —G is a leaving group such as a succinimidyl, maleimidyl, phthalimidyl, or alternatively, nitrophenyl, imidazolyl or tresyl leaving groups.

The —PEG— portion of the crosslinking agent is preferably derived from commercially available compounds having a weight average molecular weight in the range of about 1,000–15,000, preferably having a weight average molecular weight in the range of about 2,000–4,000. These compounds have been used in different types of biomedical materials because they have been demonstrated to be nontoxic as well as rapidly excreted from the body when the molecular weight is below about 30,000.

The leaving group, —G, portion of the crosslinking agent is an activated leaving group which allows the crosslinking agent to react or chemically bind to free primary or secondary amine groups of a protein. Suitable leaving groups include succinimidyl, other imides such as maleimidyl and phthalimidyl, heterocyclic leaving groups such as imidazolyl, aromatic leaving groups such as a nitrophenyl, or fluorinated alkylsulfone leaving groups such as tresyl ($CF_3—CH_2—SO_2—O—$). A preferred leaving group is the succinimidyl group because studies of the mutagenicity, oncogenicity and teratogenicity of this group suggest that the small amount of this activating group which is released as the crosslinking reaction and/or the adhesive composition cures does not present a local or systemic toxicology risk.

When used in the present composition the linking moiety, —LM—, may be several different types of divalent compounds. For example, commercially available compounds having the —PEG— portion and the —G portion linked with a saturated dicarboxylic acid such as succinic acid to give a saturated diester linking moiety. Alternatively, an unsaturated dicarboxylic acid such as fumaric, maleic,

phthalic or terephthalic acid may be used to give an unsaturated diester linking moiety. Alternatively, the linking moiety may be a readily hydrolyzable compounds such as oligomer derivatives of polylactic acid, polyglycolic acid, polydioxanone, polytrimethylene carbonate, or polycaprolactone as well as copolymers made using suitable monomers of these listed polymers.

In another embodiment of this invention an activated leaving group may be attached directly to a carbonate ester of polyethylene glycol. In this embodiment the linking moiety, —LM—, would be a carbonate group, —C(O)— between the —PEG— and —G portions of the crosslinking agent. In still other embodiments of this invention the linking moiety may be a dicarbonate such as ethylene carbonate which is prepared by linking the —PEG and —G portions with ethylene bischloroformate.

The crosslinking agents may be prepared using known processes, procedures or synthetic methods such as the procedures reported in U.S. Pat. Nos. 4,101,380 or 4,839,345, the procedure reported in International Application Ser. No. PCT/US90/02133 filed Apr. 19, 1990 or the procedure reported by Abuchowski et al., *Cancer Biochem. Biophys.*, 7:175–186 (1984). Briefly, polyethylene glycol and a suitable acid anhydride are dissolved in a suitable polar organic solvent in the presence of base and refluxed for a period of time sufficient to form a polyethylene glycol diester diacid. The diester diacid is then reacted with a leaving group such as an N-hydroxy imide compound in a suitable polar organic solvent in the presence of dicyclohexylcarbodiimide or other condensing agents and stirred at room temperature to form the desired bifunctional crosslinking agent.

Alternatively, polyethylene glycol and a suitable dicarboxylic acid chloride or bischloroformate may be dissolved in a suitable polar organic solvent for a period of time sufficient to form the mixed acid chloride polyethylene glycol ester or mixed chloroformate polyethylene glycol ester. The mixed esters may then be reacted with a compound such as an N-hydroxy imide compound in a suitable polar organic solvent and stirred at an elevated temperature for a period of time sufficient to form the desired bifunctional crosslinking agent.

It has also been found that the cure time of the present adhesive compositions may be tailored by use of buffers having different pH values. For example, by varying the pH of the buffer it is possible to change the cure rate time from about 10 seconds to less than about 10 minutes. Briefly, mixing concentrated aqueous serum albumin and crosslinking agent mixtures with higher concentrations of buffer provides the fastest cure times. It has also been found that higher concentrations of protein and crosslinking agent provide a relatively stronger, cured matrix. However, if the mixtures are too concentrated and viscosity becomes too great, these adhesive compositions are not as readily applied or may provide adhesives with undesired properties. For example, mixtures which are too viscous may not be readily applied using available applicators such as syringes or spray apparatus. In addition, if the concentration of crosslinking agent is too high, the resulting cured adhesive matrix may swell to such an extent that the strength of the matrix in the presence of water or other fluids is lowered. Further, ability to adequately mix the two components using injecting and/or spraying apparatus may be reduced.

The two component adhesive composition of the present invention may be applied to tissue in a number of different ways. For example, the adhesive may be quickly mixed together and then applied using common applicators. Alternatively the two components may be mixed together and then applied as spray. In another application method, the two parts of the adhesive are added to a dual syringe. The two barrels of the syringe are attached to a "Y" connect which is fitted to a spiral mixer nozzle. As the two components are pressed out of the syringe, they are mixed in the nozzle and may be directly applied to the tissue as needed in a relatively uniform, controlled manner. Alternatively, a spray nozzle tip, such as a TISSEEL spray tip sold by Immuno AG, Vienna, Austria for use with a two-component fibrin sealant kit, may be used in place of the spiral mixer nozzle. In this application, a fine spray of the adhesive composition is deposited on tissue as the plungers of the syringe are depressed.

The adhesive composition of the present invention may be used in a variety of current medical procedures and practices. In one application, the present adhesive composition may be used to eliminate or substantially reduce the number of sutures normally required using current practices as well as eliminate the need for subsequent removal of certain sutures. In another application, this adhesive composition may be used to attach skin grafts and to position tissue flaps or free flaps during reconstructive surgery. In still another application, this adhesive composition may be used to close gingival flaps in periodontal surgery. In all of these applications, the present adhesive composition is a thin layer of cured material which is effectively sandwiched between two adjacent layers of living tissues. Due to bioabsorbability and lack of toxicity of the adhesive composition, the healing and subsequent reattachment of the two layers of tissue to each other is not hampered.

In addition to the use of the present adhesive composition as an adhesive per se, the present composition may also be used as a sealant. When used in this application, this composition may be used to prevent air leaks now associated with pulmonary surgery or to inhibit or prevent bleeding in other surgical procedures. When used in this manner, the underlying tissue may be coated with a relatively thick layer of adhesive since the tissue itself needs to only heal on one side. The other side of the of the adhesive, when cured, simply presents a lubricous gel which will be absorbed in vivo in a relatively short period of time from about four to sixty days. In view of this property of the present adhesive composition, it may also be used to prevent unwanted tissues adhesions which are associated with current surgical procedures.

EXAMPLES

The following examples are intended to describe and illustrate the practice of the claimed invention. The examples, however, should not be construed to limit the scope of the present invention which is defined by the appended claims.

The following procedures were used to prepare several different types of bifunctional crosslinking agents. The following procedures are modifications of procedures reported in U.S. Pat. No. 4,101,380 and Abuchowski et al., cited above.

Example 1

Synthesis of Polyethylene Glycol Disuccinimidyl Succinate PEG-SS2

Polyethylene glycol, PEG, (50 g, Aldrich Chemical Company, Milwaukee, Wis., sold as 3,400 average molecular weight, GPC analysis M_n was 2,980, M_w, was 3,480) was dissolved in 1,2-dichloroethane (250 ml) containing succinic arthydride (14.7 g) and anhydrous pyridine (12 ml). The mixture was refluxed under nitrogen for three days. After

filtration and evaporation of the solvent, the residue was dissolved in 100 ml water and treated with the cation exchange resin Dowex™ 50 (H^+) (50 g) for 30 minutes. The mixture was then filtered and the Dowex™ 50 was washed with water (50 ml 1×). The combined filtrate was washed with anhydrous diethyl ether (50 ml 2×). The PEG-disuccinate was then extracted from the water phase with two 100 ml chloroform washes. Evaporation of chloroform yielded about 49 g of PEG-disuccinate.

The PEG-disuccinate was dissolved in 200 ml N,N-dimethylformamide (DMF) at 37° C. and 4.23 g of N-hydroxysuccinimide (NHS) were added to the solution. The mixture was cooled to 0° C. 7.58 g of dicyclohexylcarbodiimide (DCC) were dissolved in 50 ml DMF and added dropwise to the above solution with continuous stirring. The mixture was left at room temperature for 24 hours and filtered. 100 ml of toluene were added to the filtrate and the solution was placed in an ice bath. The desired polyethylene glycol disuccinimidyl succinate product, PEG-SS2, was precipitated by slowly adding petroleum ether. The precipitate was collected on a 10–20 micron sintered glass filter. Dissolution in toluene and precipitation with petroleum ether was repeated three times. The PEG-SS2 was further purified by dissolving in 100 ml of 0.1M pH 2.2 citrate/phosphate buffer and filtering through a 4–8 micron sintered glass filter. The PEG-SS2 was extracted with chloroform (100 ml 2×) and the solvent was evaporated under reduced pressure in a rotary evaporator. The PEG-SS2 was then dissolved in toluene and precipitated with petroleum ether, dried under vacuum overnight at room temperature, and stored in a refrigerator.

Example 2

Synthesis of N-hydroxysuccinimide Ester of Dicarboxymethyl Polyethylene Glycol

Dicarboxymethyl poly(ethylene glycol) (mol. wt. 3400) purchased from Shearwater Polymers, Inc., Huntsville, Ala. (5 g) and N-hydroxysuccinimide purchased from Sigma Chemical Co., St. Louis, Mo. (1 g) were dissolved in 30 ml of anhydrous DMF with mechanical stirring under nitrogen. The solution was cooled to 0° C. and a solution of dicyclohexylcarbodiimide (1.79 g) in 5 ml DMF was added dropwise. The stirring was continued in the cold for 3 hours then at room temperature overnight (16 hrs). Dicyclohexylurea which precipitated was removed by filtration. Toluene (100 ml) was added to the filtrate and cooled to 0° C. The product was then precipitated by addition of petroleum ether. The precipitate was collected on a sintered glass filter. Dissolution in toluene and reprecipitation with petroleum ether was repeated three times. The product was dried under vacuum in a desiccator.

Example 3

Synthesis of Polyethylene Glycol-di-oligoglycolide Disuccinimidyl Succinate

A 500 ml three neck round bottom flask was flame dried under nitrogen. 50 g of PEG (mol. wt. 3400), 300 ml of xylene, and 1 drop of 0.33M stannous ottoate solution in xylene were charged into the flask with a continuous nitrogen purge. The flask was heated to boil the solution and 50 ml of xylene were removed by distillation. The solution was then cooled to room temperature. 17 g of glycolide (Boehfinger Ingleheim KG, Ingleheim, Germany) was added to the flask and the reaction mixture was refluxed under nitrogen for 16 hours. The copolymer reaction mixture was filtered hot to remove polyglycolide homopolymer. The copolymer then precipitated from the filtrate upon cooling and collected by filtration. The copolymer was placed in a flask with 500 ml of dichloromethane and 7 g of succinyl chloride. The solution was refluxed under nitrogen overnight (16 hours). 8.5 g of N-hydroxysuccinimide was added to the flask and refluxing was continued for another overnight period. A white solid was obtained by precipitation upon cooling the solution. The product was then purified by redissolving in toluene and reprecipitating with petroleum ether several times. The final precipitate was dried under vacuum and stored in a desiccator. The structure of the product was confirmed by NMR analysis.

Example 4

Synthesis of Polyethylene Glycol-dimaleimidyl Succinate

About 12 g of PEG-disuccinate and 1 g N-hydroxymaleimide (Aldrich Chemical Co.) were placed in a 250 ml three neck round bottom flask with 50 ml of anhydrous DMF under nitrogen. The mixture was dissolved at 60° C. with mechanical stirring and cooled to 0° C. A solution of 1.82 g dicyclohexylcarbodiimide in DMF (5 ml) was added dropwise to the flask. The reaction was allowed to mix overnight under nitrogen at room temperature. Dicyclohexylurea was removed by filtration and the product was obtained by adding toluene and precipitating with petroleum ether. Dissolution in toluene and reprecipitation with petroleum ether were repeated three times. The purified product was dried under vacuum and stored in a desiccator.

Example 5

Synthesis of Polyethylene Glycol-diphthalimidyl Succinate

About 15 g of PEG-disuccinate and 1.65 g N-hydroxyphthalimide (Aldrich Chemical Co.) were placed in a 250 ml three neck round bottom flask with 30 ml of anhydrous DMF under nitrogen. The mixture was dissolved at 60° C. with mechanical stirring and cooled to 0° C. A solution of 1.82 g dicyclohexylcarbodiimide in DMF (5 ml) was added dropwise to the flask. The reaction was allowed to mix overnight under nitrogen at room temperature. Dicyclohexylurea was removed by filtration and the product was obtained by adding toluene and precipitating with petroleum ether. Dissolution in toluene and reprecipitation with petroleum ether were repeated three times. The purified product was dried under vacuum and stored in a desiccator.

Example 6

Preparation of Two Component Adhesive

The following procedure was used to prepare a two-component adhesive using a variety of protein sources, and bifunctional crosslinking agents. Aqueous solutions of a protein and a crosslinking agent as listed in Table 1 were pipetted (0.2 ml of each solution) into a porcelain test well and mixed continuously with a stainless steel rod. The cure time and physical consistency of each of the two component adhesives are also listed in Table 1.

The data indicated that fish and bovine gelatin, egg and serum albumin as well as casein protein crosslinked with PEG-SS2 provided an adhesive which was very elastic, had good adhesive strength and a relatively rapid cure rate.

TABLE 1

Protein	Bifunctional Crosslinking agent	Cure Time Consistency
Fish Gelatin Lot 23H0307 Sigma 40% 0.1 M pH 10 Carb/Bicarb	130 mg/ml PEG-SS2 3400 mw	40 sec Strong gel, very elastic, slightly sticky

TABLE 1-continued

Protein	Bifunctional Crosslinking agent	Cure Time Consistency
Fish Gelatin Lot 23H0307 Sigma 40% 0.1 M pH 10 Carb/Bicarb	260 mg/ml PEG-SS2 3400 mw	40 sec Strong gel, very elastic, slightly sticky
Fish Gelatin Lot 23H0307 Sigma 40% 0.1 M pH 10 Carb/Bicarb	130 mg/ml PEG-SS2 10,000 mw	120 sec Soft gel, very sticky
Fish Gelatin Lot 23H0307 Sigma 40% 0.1 M pH 10 Carb/Bicarb	260 mg/ml PEG-SS2 10,000 mw	110 sec Soft gel to elastic, moderately sticky
Gelatin Bovine Skin Lot 53H0271 Sigma 40% 0.1 M pH 10 Carb/Bicarb	130 mg/ml PEG-SS2 3400 mw	40 sec Soft gel, not elastic
Gelatin Bovine Skin Lot 53H0271 Sigma 40% 0.1 M pH 10 Carb/Bicarb	260 mg/ml PEG-SS2 3400 mw	40 sec Soft gel, not elastic
Gelatin Bovine Skin Lot 53H0271 Sigma 40% 0.1 M pH 10 Carb/Bicarb	130 mg/ml PEG-SS2 10,000 mw	40 sec Soft gel, not elastic
Gelatin Bovine Skin Lot 53H0271 Sigma 40% 0.1 M pH 10 Carb/Bicarb	260 mg/ml PEG-SS2 10,000 mw	120 sec Soft gel, not elastic
Casein pH 9.4 12.6% Carb/Bicarb	130 mg/ml PEG-SS2 3400 mw	40 sec Strong gel, elastic, not sticky
Poly-L-Lysine 50 mg/ml H_2O 300,000 mw Carb/Bicarb	130 mg/ml PEG-SS2 3400 mw	20 sec Waxy, no adhesive strength
Poly-L-Lysine 50 mg/ml H_2O 300,000 mw Carb/Bicarb	260 mg/ml PEG-SS2 3400 mw	15 sec Waxy, no adhesive strength
Poly-L-Lysine 50 mg/ml H_2O 300,000 mw Carb/Bicarb	130 mg/ml PEG-SS2 10,000 mw	10 sec Waxy, no adhesive strength
Poly-L-Lysine 50 mg/ml H_2O 300,000 mw Carb/Bicarb	260 mg/ml PEG-SS2 10,000 mw	10 sec Waxy, no adhesive strength
Chicken Egg Albumin 40% 0.08 M pH 10 Carb/Bicarb	130 mg/ml PEG-SS2 3400 mw	210 sec soft, tacky
Rabbit Serum Albumin (RSA) Sigma Lot 19F9301 40% 0.1 M pH 10 Carb/Bicarb	130 mg/ml PEG-SS2 3400 mw	20 sec Very elastic, good adhesive strength, not sticky
Human Serum Albumin (HSA) Sigma Lot 63H9041 40% 0.1 M pH 10 Carb/Bicarb	130 mg/ml PEG-SS2 3400 mw	20 sec Very elastic, good adhesive strength, not sticky
HSA Sigma Lot 63H9041 40% 0.1 M pH 10 Carb/Bicarb	130 mg/ml PEG-SS2 3400 mw	20 sec Very elastic, good adhesive strength, not
HSA	260 mg/ml	10 sec Very elastic,

TABLE 1-continued

Protein	Bifunctional Crosslinking agent	Cure Time Consistency
Sigma Lot 63H9041 40% 0.1 M pH 10 Carb/Bicarb	PEG-SS2 3400 mw	good adhesive strenght, not sticky
HSA Sigma Lot 63H9041 40% 0.1 M pH 10 Carb/Bicarb	130 mg/ml PEG-SS2 10,000 mw	30 sec Very elastic, slight adhesive strength, very sticky
HSA Sigma Lot 63H9041 40% 0.1 M pH 10 Carb/Bicarb	260 mg/ml PEG-SS2 10,000 mw	25 sec Very elastic, slight adhesive strength, very sticky
HSA Baxter Healthcare Corp. Lot 2837A238AA Carb/Bicarb	130 mg/ml PEG-dimaleimidyl succinate Example 4	20 sec Turned brown upon curing, hard gel, not sticky
HSA Baxter Lot 2837A238AA Carb/Bicarb	130 mg/ml PEG-diphthalimidyl succinate Example 5	10 sec Turned red upon curing, hard gel, not sticky
HSA Baxter Lot 2837A238AA Carb/Bicarb	130 mg/ml PEG-dicaboxymethyl disuccinimidyl Example 2	8 sec Hard gel, not sticky, no color change
HSA Baxter Lot 2837A238AA Carb/Bicarb	130 mg/ml PEG-dioliglycolide disuccinimidyl succinate Example 3	40 sec Hard gel, not sticky, no color change
HSA Baxter Lot 2837A238AA Carb/Bicarb	130 mg/ml PEG-disuccinimidyl propionate PED(SPA)2	30 sec Hard gel, not sticky, no color change
HSA Baxter Lot 2837A238AA Carb/Bicarb	260 mg/ml PEG-disuccinimidyl propionate PEG(SPA)2	40 sec Hard gel, not sticky, no color change
HSA Baxter Lot 2837A238AA Carb/Bicarb	130 mg/ml PEG-dioxycarbooyl imidazole PEG(CDI)2	48 hrs Hard gel, not (cure) sticky, no color change
HSA Baxter Lot 2837A238AA Carb/Bicarb	130 mg/ml PEG-dinitrophenyl carbonate PEG(NPC)2	140 sec Hard gel, not sticky, changed to bright yellow color
HSA Baxter Lot 2837A238AA Carb/Bicarb	260 mg/ml PEG-dinitrophenyl carbonate PEG(NPC)2	140 sec Hard gel, not sticky, changed to bright yellow color
HSA Baxter Lot 2837A238AA Carb/Bicarb	130 mg/ml PEG-ditresylate PEG(tres)2	8 hrs Hard gel, not (viscous) sticky, no color 24 hrs change (cure)
HSA Baxter Lot 2837A238AA Carb/Bicarb	130 mg/ml PEG-diglycidyl ether PEG(epox)2	72 hrs Hard gel, not (cure) sticky, no color change
HSA Baxter Lot 2837A338AA Carb/Bicarb	130 mg/ml PEG-dialdehyde PEG(ald)2	no cure Liquid

mw = weight average molecular weight

Example 7

Effect of Buffer and pH

Two component adhesives were prepared according to the process described in Example 6 except that the pH of the buffer in the protein solution was changed as listed in Table 2. The data indicate that a preferred pH range is about 8.44–10.0.

TABLE 2

Protein	Crosslinking agent PEG-SS2	Cure Time	Constistency
HSA Baxter Lot 2837A238AA 40% 0.1 M pH 7.4 Carb/Bicarb	130 mg/ml 3400 mw	10 min	Initially softer adhesive, hardens with aging
HSA Sigma Lot 63H9041 40% 0.1 M pH 8.44 Carb/Bicarb	130 mg/ml 3400 mw	20 sec	Very elastic, good adhesive strength not sticky
HSA Sigma Lot 63H9041 40% 0.15 M pH 9.07 Carb/Bicarb	130 mg/ml 3400 mw	10 sec	Hard gel, not sticky
HSA Sigma Lot 63H9041 40% 0.2 M pH 9.52 Carb/Bicarb	130 mg/ml 3400 mw	5 sec	Hard gel, not sticky
HSA Sigma Lot 63H9041 40% 0.2 M pH 9.52 Carb/Bicarb	260 mg/ml 3400 mw	5 sec	Hard gel, not sticky
HSA Sigma Lot 63H9041 40% 0.2 M pH 9.52 Carb/Bicarb	130 mg/ml 10,000 mw	7 sec	Elastic to hard gel, slightly sticky
HSA Sigma Lot 63H9041 40% 0.2 M pH 9.52 Carb/Bicarb	260 mg/ml 10,000 mw	7 sec	Elastic to hard gel, slightly sticky
HSA Baxter Lot 2837A238AA 40% 0.1 M pH 10 Carb/Bicarb	130 mg/ml 3400 mw	25 sec	Very elastic, not sticky
HSA Sigma Lot 63H9041 40% 0.1 M pH 10 Carb/Bicarb	130 mg/ml 3400 mw	25 sec	Very elastic, not sticky

mw = weight average molecular weight

Example 8

Effect of Crosslinking Agent on Adhesive Strength

A 30% HSA (Human Serum Albumin) solution from Sigma Chemical Co. and a 25% HSA solution from Baxter Healthcare, Inc. were dialyzed against 0.1M carbonate/bicarbonate pH 10 buffer at 4° C. overnight and concentrated to about 40% by ultra-filtration through a 50,000 molecular weight cut-off cellulose ester disc membrane (Spectrum Medical Industries, Inc.) in a pressure filtration cell under nitrogen at 60 psig. The final concentration was calculated based on the volume of collected filtrate. The maximum concentration obtained under these conditions during overnight ultra-filtration was typically 42–45%. The RSA (Rabbit Serum Albumin) from Sigma and RSA crystallized protein from ICN Biomedical, Inc. were dissolved in 0.1M pH 10 carbonate/bicarbonate buffer and concentrated to 40% by the same method used for HSA.

Various concentrations of PEG-SS2 (3,400 mw and 10,000 mw) were prepared in deionized water. The albumins and crosslinking agent solutions were delivered in equal volume using a 1 ml dual syringe. The syringe tips were fitted with a Y connector which connected to a specially machined TEFLON adaptor inserted into a 1.8 in.x0.187 in. (4.57 cmx0.475 cm) dia. spiral mixer nozzle (TAH Industries, Inc., Robbinsville, N.J., part no. 150-312). The adhesive mixture was injected through the mixer directly onto the test substrate for adhesion testing.

Freshly excised guinea pig skin was cut into strips and a polystyrene window with an opening of 0.5x1.0 inches (1.27 cmx2.54 cm) was placed on one end of the strip to contain the glue in a specific region. Upon filling the window with glue it was covered with another strip of guinea pig skin. A 500 g steel weight was placed on top of this assembly for about one minute. The sample was peeled apart in the jaws of a computer controlled mechanical testing machine (880 Material Test System, MTS System, Inc., Minneapolis, Minn.) set at a strain rate of 0.8 in./min. (2 cm/min.) with a gage length of 1 in. (2.54 cm) and a 5 lbs. (2.27 kg) load cell. Peel force was recorded after the initiation of adhesive failure as the constant force require to continue peeling as shown in FIG. 1. Four replicates were performed for each test condition. The results of this test are listed in FIG. 2.

Example 9

Measurement of Adhesive Sealant Burst Strength

A pressurization assembly illustrated in FIG. 3 was used to test the bursting strength of materials used to seal standardized holes or slits in test membranes. This assembly included an aluminum pressure vessel (1) having a 35 mm inside diameter fitted with a millivolt output type pressure transducer (2) with a range of 0 to 15 psig (MODEL PX236, Omega Engineering, Inc., Stamford, Conn.) and a pressure inlet port (3). To perform a test, about a 5 mm diameter hole (4) (or other standardized defect) was cut in the center of a test membrane (5) using a die cutter. The membrane was then placed on a piece of 0.4 mm thick TEFLON film with the hole in the membrane centered in a larger (24 mm diameter) hole in the TEFLON film. The TEFLON film was then placed on a flat surface with the membrane side down and adhesive sealant test material was applied to fill the hole in the film. A solid TEFLON block was then quickly placed over the sealant prior to cure so that the TEFLON film served as a spacer to create a layer of sealant exactly 0.4 mm thick. After the desired cure time elapsed, the TEFLON block was inverted and the membrane was carefully peeled off to obtain a circular patch of sealant (6) covering the hole in the membrane. The test membrane with sealed defect was then mounted onto the open end of the pressure vessel (7) by placing it between two rubber washers (8) and then between two metal washers (9). An air tight seal was obtained by screwing the threaded cover (10) onto the matching threads (11) of the pressure vessel. The opening in the cover (12) was also 35 mm in diameter which, in combination with the 35 mm inside diameter washers, provided a fixed membrane surface area for pressure testing.

Two types of membranes were used, either a collagen membrane or a freshly excised porcine pericardium sample. The porcine pericardium sample was either used immediately upon harvest or after storage in a moisture-proof container at 4° C. for no longer than 24 hours. Under these conditions there was no discernible difference in sealant performance based on storage time of that tissue.

The pressurization sequence was initiated by injecting air into the pressure inlet at a fixed rate of one cubic centimeter per second using a syringe pump (Sage Instruments Model 351, Orion Research, Inc.). The pressure transducer was connected to a digital strain gauge meter (Omega Model DP205-S, Omega. Engineering, Inc.) programmed to read pressure (ram mercury) and to display the peak pressure value at the time of adhesive sealant rupture. Replicate tests

gave reproducible peak pressure values and the standard deviation was reported in each case.

Pressure tests were performed with an adhesive composition of 40% HSA (or RSA) in 0.08M carbonate/bicarbonate buffer at different pH values with 3,400 m.wt. PEG-SS2 (130 mg/ml) on collagen and pericardium membranes. The results listed in Table 3 demonstrate excellent sealant performance with typical peak pressure values of about 130 mm Hg.

In addition, the peak pressure for the above sealants after soaking in saline solution was measured. The test was performed as described above except that the surface of the sealant coated membrane was flooded with saline for up to a time period of 90 minutes before pressurization. Although the sealant hydrogel swelled to about double in thickness, substantial retention of sealant performance was retained.

Table 4 shows the data obtained by testing a variety of proteins including fish skin gelatin, chicken egg albumin, and fibrinogen. Fibrinogen mixed with thrombin ("fibrin glue", BERIPLAST-P sealant, Behringwerke, Marburg, Germany) was also used as a control sealant material. None of these materials performed as well as the serum albumin examples. The main disadvantage was the cure and aging time required to achieve significant strength. In particular, chicken egg albumin required twenty-five minutes of post cure aging to achieve the same burst strength obtained from serum albumin aged for less than five minutes.

The same process was repeated for additional 25% HSA solutions by dialyzing against 0.08M carbonate/bicarbonate buffers at pH 9 and pH 8. A pH 7 solution of HSA was obtained by concentration of the original 25% HSA solution to 40% by ultrafiltration. The crosslinking agent solution PEG-SS2 (3400 mw) was 130 mg dissolved in one ml deionized water. The albumin and crosslinking agent solutions were delivered in equal volume using a one ml dual syringe as in Example 8. The pressure tests were performed as above using collagen membrane except that the sealant hydrogel was aged before testing. The results are also listed in Table 4. These data demonstrate that optimal pressure test values are achieved faster with increasing pH of the albumin solution. Moreover, the resultant cured sealant obtained after complete curing has taken place is unexpectedly higher with higher pH of the albumin solution.

TABLE 3

Tissue	Tissue Opening	Adhesive Composition	Burst Preasure (mm Hg)
Collagen	4.56 mm dia. hole	HSA:PEG-SS2	150
Collagen	5 mm slit	HSA:PEG-SS2	112
Collagen	4.56 mm dia. hole	RSA:PEG-SS2	130
Collagen	5 mm slit	RSA-PEG-SS2	125
Porcine Pericardium	4.56 mm dia. hole	HSA:PEG-SS2	155
Porcine Pericardium	5 mm slit	HSA:PEG-SS2	130
Porcine Pericardium	4.56 mm dia. hole	RSA:PEG-SS2	125
Porcine Pericardium	5 mm slit	RSA:PEG-SS2	130

TABLE 4

Pressure Test of Different Proteins Using Collagen and Pericardium
HSA: 40% 0.08 M Carb/Bicarb Buffer in Saline Lot #2837a328AA
RSA: 40% 0.08 M Carb/Bicarb Buffer in Saline Lot #82-451-0050 INC
PEG-SS2: 3400 mw lot #103128-110 (130 mg/ml)
Defect: 4.56 mm hole
Air Flow Rate: 1 cc/s

Protein	Crosslinker	Membrane	Pressure (mm Hg) Ave	St dev	Comments
HSA pH 10	PEG-SS2	Collagen	149	9	No bubbles
		Pericardium	154	4	5 min after curing
		Pericardium	196	5	10 min after curing
HSA pH 10	PEG-SS2	Collagen	144		5 min after curing
			155		10 min after curing
			162		20 min after curing
HSA pH 9	PEG-SS2	Collagen	108		5 min after curing
			114		10 min after curing
			116		20 min after curing
HSA pH 8	PEG-SS2	Collagen	36		5 min after curing
			78		10 min after curing
			90		20 min after curing
HSA pH 7	PEG-SS2	Collagen	30		10 min after curing
			52		20 min after curing
RSA pH 10	PEG-SS2	Collagen	134	5	No bubbles
		Pericardium	126	10	5 min after curing
		Pericardium	194	9	10 min after curing
Fish Gelatin pH 10 40% (Sigma)	PEG-SS2	Collagen	34	2	10 min after curing
Chicken Egg Albumin pH 10 40% (Sigma)	PEG-SS2	Collagen	14	3	10 min after curing
			151	5	45 min after curing

TABLE 4-continued

Pressure Test of Different Proteins Using Collagen and Pericardium
HSA: 40% 0.08 M Carb/Bicarb Buffer in Saline Lot #2837a328AA
RSA: 40% 0.08 M Carb/Bicarb Buffer in Saline Lot #82-451-0050 INC
PEG-SS2: 3400 mw lot #103128-110 (130 mg/ml)
Defect: 4.56 mm hole
Air Flow Rate: 1 cc/s

Protein	Crosslinker	Membrane	Pressure (mm Hg) Ave	St dev	Comments
Fibrin Glue (BERIPLAST-P) Used according to mfg. instructions		Pericardium	8	2	5 min after curing with saline, glue slid off easily
			39	2	5 min after curing without saline, leaked underneath
Bovine Fibrinogen pH 10 15% (Sigma)	PEG-SS2	Collagen	8	2	5 min after curing
			8	2	60 min after curing, glue slid off easily

Example 10

Use of a Two Component Adhesive Sealant in General and Thoracic Surgery

An anesthetized pig was used as an experimental model for thoracic surgical complications such as staple line leaks during lung and bronchus resections, bronchopleural fistulas, and other conditions resulting in pneumothorax.

The two component adhesive included Part A, a 40% HSA prepared by dialysis of commercially available HSA (25% Solution, BUMINATE 25%, Baxter Healthcare Corp., Hyland Division, Glendale, Calif.) against 0.08M pH 10 carbonate/bicarbonate buffer followed by concentration to 40% by ultrafiltration at 50 psi using a 50,000 molecular weight cut-off cellulose ester disc membrane and Part B, a 130 mg/ml solution of 3,400 m.wt. PEG-SS2 dissolved in sterile distilled water no more than 30 minutes prior to use. The PEG-SS2 was synthesized and purified as described in Example 1.

A stab wound was made on the lung of an anesthetized pig with a scalpel which resulted in significant air leakage during inspiration as evidenced by bubbling of air through irrigation fluid administered to the site. The wound was blotted with gauze to remove blood and fluid. The respirator was turned off and the adhesive was applied as a sealant using a dual syringe (Behring PANTAJECT syringe, Behringwerke, Marburg, Germany) equipped with a spiral mixing tip. After a 20 second cure time ventilation was restored and the lung was again covered with irrigation fluid. No air leaks were observed.

A functional end-to-end anastomosis in pig intestine was conducted using a standard stapling procedure. The adhesive material described above was applied to the staple lines. This resulted in a clear, adherent hydrogel coating which appeared to seal the anastomotic line.

Under these conditions it was observed that anastomotic lines coated with the sealant were air tight whereas anastomotic lines not sealed were not air tight.

Example 11

Use of Two Component Adhesive to Prevent Post-Surgical Adhesions

The tissue sealant hydrogel tested was a two part liquid system. Part A was a sterile 40% (w/v) solution of human serum albumin in isotonic pH 10 carbonate buffer (0.1M). Part B was a 400 mg/ml solution of 10,000 molecular weight PEG-SS2 (polyethylene glycol disuccinimidyl succinate) in sterile distilled water prepared just prior to use. Solutions A and B were mixed in equal volumes with a dual syringe system connected to a static mixing head (Tah Industries, Inc.).

Post-surgical adhesion prevention evaluation of this sealant formulation was initiated in a series of ten female rabbits. A 2x2 cm area of the abdominal wall was excised down to the fascia on each side of the abdominal cavity exposed by a midline laparotomy incision. The uterine horns were injured by scraping 20 times with a no. 10 scalpel blade. Each animal served as its own control by randomly applying test material to only one of the abdominal wall injuries. The uterine horns were then attached with two stitches to the abdominal wall within a few millimeters of the edge of the wound closest to the laparotomy incision.

Two weeks after surgery the rabbits were examined in order to evaluate and score the extent, type, and tenacity of adhesions present on the abdominal wall injury sites. These results are shown in Table 5. The rating system used to obtain these scores is shown in Table 6. Although technical difficulties were encountered as noted in Table 5, the test material clearly provided an unexpected benefit in both the prevention of adhesions and a reduction in their severity without the presence of a known active ingredient.

TABLE 5

Scoring of Adhesions Formed in Material Evaluation

	Characteristic					
	Extent		Type		Tenacity	
Animal	Control	Treatment	Control	Treatment	Control	Treatment
BAM 8	2	0+	3	0+	3	0+
BAM 9	3	1	3	1	3	1
BAM 10	0+	1	0+	3	0+	2
BAM 11	0*	0	0*	0	0*	0
BAM 12	4	4	3	3	3	3
BAM 13	2	1	3	2	3	2
BAM 14	1*	0	3*	0	3*	0
BAM 15	1	0**	1	0**	2	0**
BAM 16	1	0*	1	0*	2	0*

TABLE 5-continued

Scoring of Adhesions Formed in Material Evaluation						
	Characteristic					
	Extent		Type		Tenacity	
Animal	Control	Treatment	Control	Treatment	Control	Treatment
BAM 17	1	0*	1	0*	2	0*
Average	1.5	0.7	1.5	0.9	2.1	0.8

*Uterine horn tacked to abdominal wall with only one suture
**Uterine horn no longer sutured to abdominal wall
+Fascia removed with peritoneacum and muscle layers

TABLE 6

Characteristics	Adhesion Score
Extent (% sidewall Evolvement)	
None	0
≤25	1
≦50	2
≤75	3
>75	4
Type	
None	0
Filmy, no vessels (transparent)	1
Opaque, no vessels (translucent)	2
Opaque, small vessels present grossly	3
Opaque, larger vessels present grossly	4
Tenacity	
None	0
Adhesions essentially fell apart	1
Adhesions lysed with traction	2
Adhesions required sharp dissection for lysis	3

We claim:

1. An adhesive composition consisting essentially of

i) a first aqueous mixture of about 20–60 wt/vol % serum albumin in about 0.01–0.25 molar buffer at a pH in a range of about 8.0–11.0,

ii) a second aqueous mixture of about 50–800 mg/ml of a crosslinking agent having a molecular weight in a range of about 1,000–15,000, wherein the crosslinking agent is of the formula

G—LM—PEG—LM—G

wherein —PEG— is a diradical fragment represented by the formula

—O—(CH_2—CH_2—O—)$_a$—

where a is an integer from 20–300;

wherein —LM— is a diradical fragment selected from the group consisting of a carbonate diradical of the formula[,] —C(O)—, a monoester diradical of the formula[,] —(CH_2)$_b$C(O)— where b is an integer from 1–5, a diester diradical of the formula[,] —C(O)—(CH_2)$_c$—C(O)— where c is an integer from 2–10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula —C(O)—O—(CH_2)$_d$—O—C(O)— where d is an integer from 2–10, and an oligomeric diradical represented by the formulas —R—C(O)—, —R—C(O)—(CH_2)$_c$—C(O)—, or —R—C(O)—O—(CH_2)$_d$—O—C(O)— where c is an integer from 2–10, d is an integer from 2–10, and R is a polymer or copolymer having 1–10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone and p-dioxanone; [and]

wherein —G is a leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, [or] *and* tresyl[,]; and

wherein a combination of the first and second mixtures is initially liquid and then cures on the surface of tissue to give a flexible, substantive matrix which bonds to the tissue and bas a burst strength greater than about 10 mmHg.

2. The adhesive [mixture] *composition* of claim 1 wherein the protein in the first mixture is about 35–45 wt/vol % serum albumin.

3. The adhesive composition of claim 1 wherein the serum albumin is human serum albumin.

4. The adhesive composition of claim 1 wherein the buffer is 0.05–0.15 molar carbonate/bicarbonate buffer at a pH of about 9.0–10.5.

5. The adhesive composition of claim 1 wherein the second aqueous mixture is about 50–300 mg/ml of a crosslinking agent having a molecular weight in a range of about 1,000–5,000.

6. The adhesive composition of claim 1 wherein the ratio of a volume of the first mixture to a volume of the second mixture is in a range of about 1:10 to about 10:1.

7. The adhesive composition of claim 1 wherein —LM— is an oligomeric diradical —R—C(O)—(CH_2)$_c$—C(O)— where c is an integer from 2–10 and R is a polymer or copolymer having 1–10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone and p-dioxanone.

8. The adhesive composition of claim 1 wherein —G is succinimidyl.

9. An in vivo method of adhering tissue comprising the steps of topically applying and bonding an adhesive [mixture] *composition* of claim 1 to the tissue.

10. An in vivo method of sealing air leaks in pulmonary tissues comprising the step of topically applying and curing the adhesive [mixture] *composition* of [claims] *claim* 1 to an air leak site in the pulmonary tissue.

11. An in vivo method to prevent post-surgical adhesions comprising the step of topically applying and curing the adhesive [mixture] *composition* of [claims] *claim* 1 to tissue surrounding a surgical site.

12. An in vivo method to seal tissue comprising the step of topically applying and bonding the adhesive [mixture] *composition* of [claims] *claim* 1 to tissue to prevent or control blood or other fluid leaks.

13. The adhesive composition of claim 1 wherein the second aqueous mixture is about 300–800 mg/ml of a crosslinking agent having a molecular weight in a range of about 5,000–15,000.

14. The adhesive composition of claim 13 wherein —LM— is a diester diradical of the formula —C(O)—(CH_2)$_2$—C(O)—.

15. The adhesive [mixture] *composition* of claim 1 wherein —LM— is a diester diradical of the formula[,] —C(O)—(CH_2)$_c$—C(O)— where c is an integer from 2–10 and where the aliphatic portion of the diradical may be saturated or unsaturated.

16. The adhesive composition of claim [15] *1* wherein —LM— is [a] *an* oligomeric diradical derived from polyglycolic acid.

17. A method of making a tissue adhesive consisting of the step of forming a mixture of

i) a first aqueous mixture of about 20–60 wt/vol % serum albumin in about 0.01–0.25 molar buffer at a pH in a range of about 8.0–11.0,

ii) a second aqueous mixture of about 50–800 mg/ml of a crosslinking agent having a molecular weight in a range of about 1,000–15,000, wherein the crosslinking agent is of the formula

G—LM—PEG—LM—G

wherein —PEG— is a diradical fragment represented by the formula

$$—O—(CH_2—CH_2—O—)_a—$$

where a is an integer from 20–300;

wherein —LM— is a diradical fragment selected from the group consisting of a carbonate diradical of the formula[,] —C(O)—, a monoester diradical of the formula[,] —$(CH_2)_b$C(O)— where b is an integer from 1–5, a diester diradical of the formula[,] —C(O)—$(CH_2)_c$—C(O)— where c is an integer from 2–10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula —C(O)—O—$(CH_2)_d$—O—C(O)— where d is an integer from 2–10, and an oligomeric diradical represented by the formulas —R—C(O)—, —R—C(O)—$(CH_2)_c$—C(O)—, or —R—C(O)—O—$(CH_2)_d$—O—C(O)— where c is an integer from 2–10, d is an integer from 2–10, and R is a polymer or copolymer having 1–10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone and p-dioxanone; [and]

wherein —G is a leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl [or], *and* tresyl[,]; and

wherein a combination of the first and second mixtures is initially liquid and then cures on the surface of tissue to give a flexible, substantive matrix which bonds to the tissue and has a burst strength greater than about 10 mmHg.

18. A method of treating tissue to prevent or control air or fluid leaks comprising:

providing a composition to tissue, said composition including a serum albumin protein at about 20–60 wt/vol % and a crosslinking agent at about 50–800 mg/ml, said crosslinking agent having a polyoxyethylene chain portion and an activated leaving group which allows the crosslinking agent to react with said protein and having a molecular weight in a range of about 1,000–15,000; and

curing said composition on the tissue to bond said composition to the tissue and to provide a substantive cured matrix that has a burst strength greater than about 10 mm Hg.

19. The method of claim 18 wherein said composition is cured to produce the matrix in less than about 10 minutes.

20. The method of claim 18 wherein said composition is cured to produce the matrix in less than about one minute.

21. The method of claim 18 wherein said composition is cured to produce the matrix in about ten seconds.

22. The method of claim 18 comprising providing the composition to the tissue using a syringe.

23. The method of claim 18 comprising providing the composition to the tissue using a dual syringe.

24. The method of claim 18 comprising providing the composition to the tissue using a spray apparatus.

25. The method of claim 18 wherein the matrix is resorbed.

26. The method of claim 25 wherein the matrix is resorbed in about four to sixty days.

27. The method of claim 18 comprising curing the composition such that the peel strength of the matrix is about 0.08 lb/in or more.

28. The method of claim 18 wherein the matrix has a burst pressure of about 34 mmHg or greater.

29. The method of claim 28 wherein the matrix has a burst pressure of about 90 mmHg or greater.

30. The method of claim 29 wherein the matrix has a burst pressure of about 130 mmHg or greater.

31. The method of claim 18 comprising providing a composition wherein the crosslinking agent has a molecular weight in a range of about 1,000–5,000.

32. The method of claim 18 comprising providing a composition wherein the activated leaving group is an N-hydroxy imide.

33. The method of claim 32 comprising providing a composition wherein the activated leaving group is N-hydroxy succinimide.

34. The method of claim 18 further comprising mixing a first mixture and a second mixture to form the composition and applying said composition to the tissue,

wherein the first mixture includes about 20–60 wt/vol % of the protein in about 0.01–0.25 molar buffer at pH in a range of about 8.0–11.0 and the second mixture includes about 50–800 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000–15,000.

35. The method of claim 34 wherein the crosslinking agent is of the formula

—G—LM—PEG—LM—G

wherein:

—PEG— is a diradical fragment represented by the formula

$$—O—(CH_2—CH_2—O—)_a—$$

where a is an integer from 20–300;

—LM— is a diradical fragment selected from the group consisting of a carbonate diradical of the formula —C(O)—, a monoester diradical of the formula —$(CH_2)_b$C(O)— where b is an integer from 1–5, a diester diradical of the formula —C(O)—$(CH_2)_c$—C(O)— where c is an integer from 2–10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula —C(O)—O—$(CH_2)_d$—O—C(O)— where d is an integer from 2–10, and an oligomeric diradical represented by the formulas —R—C(O)—, —R—C(O)—$(CH_2)_c$—C(O)—, or —R—C(O)—O—$(CH_2)_d$—O—C(O)— where c is an integer from 2–10, d is an integer from 2–10, and R is a polymer or copolymer having 1–10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

—G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

36. The method of claim 35 wherein the protein in the first mixture is about 35–45 wt/vol % serum albumin.

37. The method of claim 36 wherein the buffer is 0.05–0.15 molar carbonate/bicarbonate buffer at a pH of about 9.0–10.5.

38. The method of claim 35 wherein the second mixture is about 50–300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000–5,000.

39. The method of claim 35 wherein the ratio of a volume of the first mixture to a volume of the second mixture is in a range of about 1:10 to about 10:1.

40. The method of claim 35 wherein —LM— is an oligomeric diradical —R—C(O)—$(CH_2)_c$—C(O)— where c is an integer from 2–10 and R is a polymer or copolymer having 1–10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone.

41. The method of claim 35 wherein —G is succinimidyl.

42. The method of claim 35 wherein the second mixture includes about 300–800 mg/ml of a crosslinking agent having a molecular weight in a range of about 5,000–15,000.

43. The method of claim 35 wherein —LM— is a diester diradical of the formula —C(O)—$(CH_2)_2$—C(O)—.

44. The method of claim 35 wherein —LM— is a diester diradical of the formula —C(O)—$(CH_2)_c$—C(O)— where c is an integer from 2–10 and where the aliphatic portion of the diradical may be saturated or unsaturated.

45. The method of claim 35 wherein —LM— is an oligomeric diradical derived from polyglycolic acid.

46. The method of claim 18 comprising treating tissue to prevent or control a fluid leak.

47. The method of claim 46 wherein the fluid leak is a blood leak.

48. The method of claim 18 wherein the tissue includes an air leak.

49. The method of claim 48 wherein the air leak is in a pulmonary system.

50. A method of treating tissue to prevent formation of an adhesion comprising:

providing a composition to tissue, said composition including a serum albumin protein at about 20–60 wt/vol % and a crosslinking agent of about 50–800 mg/ml, said crosslinking agent having a polyoxyethylene chain portion and an activated leaving group which allows the crosslinking agent to react with said protein and having a molecular weight in the range of about 1,000–15,000; and

curing said composition on the tissue to bond said composition to the tissue and to provide a substantive cured matrix that has a burst strength greater than about 10 mm Hg.

51. The method of claim 50 wherein said composition is cured to produce the matrix in less than about 10 minutes.

52. The method of claim 50 wherein said composition is cured to produce the matrix in less than about one minute.

53. The method of claim 50 wherein said composition is cured to produce the matrix in about ten seconds.

54. The method of claim 50 comprising providing the composition to the tissue using a syringe.

55. The method of claim 50 comprising providing the composition to the tissue using a dual syringe.

56. The method of claim 50 comprising providing the composition to the tissue using a spray apparatus.

57. The method of claim 50 wherein the matrix is resorbed.

58. The method of claim 57 wherein the matrix is resorbed in about four to sixty days.

59. The method of claim 50 comprising curing the composition such that the peel strength of the matrix is about 0.08 lb/in or more.

60. The method of claim 50 wherein the matrix has a burst pressure of about 34 mmHg or greater.

61. The method of claim 60 wherein the matrix has a burst pressure of about 90 mmHg or greater.

62. The method of claim 61 wherein the matrix has a burst pressure of about 130 mmHg or greater.

63. The method of claim 50 comprising providing a composition wherein the crosslinking agent has a molecular weight in a range of about 1,000–5,000.

64. The method of claim 50 comprising providing a composition wherein the activated leaving group is an N-hydroxy imide.

65. The method of claim 64 comprising providing a composition wherein the activated leaving group is N-hydroxy succinimide.

66. The method of claim 50 further comprising mixing a first mixture and a second mixture to form the composition and applying said composition to the tissue,

wherein the first mixture includes about 20–60 wt/vol % of the protein in about 0.01–0.25 molar buffer at a pH in a range of about 8.0–11.0 and the second mixture includes about 50–800 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000–15,000.

67. The method of claim 66 wherein the crosslinking agent is of the formula

G—LM—PEG—LM—G

wherein:

—PEG— is a diradical fragment represented by the formula

—O—$(CH_2$—CH_2—O—$)_a$—

where a is an integer from 20–300;

—LM— is a diradical fragment selected from the group consisting of a carbonate diradical of the formula —C(O)—, a monoester diradical of the formula —$(CH_2)_b$C(O)— where b is an integer from 1–5, a diester diradical of the formula —C(O)—$(CH_2)_c$—C(O)— where c is an integer from 2–10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula —C(O)—O—$(CH_2)_d$—O—C(O)— where d is an integer from 2–10, and an oligomeric diradical represented by the formulas —R—C(O)—, —R—C(O)—$(CH_2)_c$—C(O)—, or —R—C(O)—O—$(CH_2)_d$—O—C(O)— where c is an integer from 2–10, d is an integer from 2–10, and R is a polymer or copolymer having 1–10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

—G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

68. The method of claim 67 wherein the protein in the first mixture is about 35–45 wt/vol % serum albumin.

69. The method of claim 68 wherein the buffer is 0.05–0.15 molar carbonate/bicarbonate buffer at a pH of about 9.0–10.5.

70. The method of claim 67 wherein the second mixture is about 50–300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000–5,000.

71. The method of claim 67 wherein the ratio of a volume of the first mixture to a volume of the second mixture is in a range of about 1:10 to about 10:1.

72. The method of claim 67 wherein —LM— is an oligomeric diradical —R—C(O)—$(CH_2)_c$—C(O)— where c is an integer from 2–10 and R is a polymer or copolymer having 1–10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone.

73. The method of claim 67 wherein —G is succinimidyl.

74. The method of claim 67 wherein the second mixture includes about 300–800 mg/ml of a crosslinking agent having a molecular weight in a range of about 5,000–15,000.

75. The method of claim 67 wherein —LM— is a diester diradical of the formula —C(O)—$(CH_2)_2$—C(O)—.

76. The method of claim 67 wherein —LM— is a diester diradical of the formula —C(O)—$(CH_2)_c$—C(O)— where c is an integer from 2–10 and where the aliphatic portion of the diradical may be saturated or unsaturated.

77. The method of claim 67 wherein —LM— is an oligomeric diradical derived from polyglycolic acid.

78. The method of claim 50 wherein the composition is provided to tissue at a surgical site.

79. The method of claim 50 wherein the composition is provided on a surface of an internal organ.

80. A method of treating tissue to bind layers of tissue together comprising:

providing a composition to tissue, said composition including a serum albumin protein at about 20–60 wt/vol % and a crosslinking agent at about 50–800 mg/ml, said crosslinking agent having a polyoxyethylene chain portion and an activated leaving group which allows the crosslinking agent to react with said protein and having a molecular weight in the range of about 1000–15,000; and

curing said composition on the tissue to bond said composition to the tissue and to provide a substantive cured matrix that has a burst strength of greater than about 10 mm Hg.

81. The method of claim 80 wherein said composition is cured to produce the matrix in less than about 10 minutes.

82. The method of claim 80 wherein said composition is cured to produce the matrix in less than about one minute.

83. The method of claim 80 wherein said composition is cured to produce the matrix in about ten seconds.

84. The method of claim 80 comprising providing the composition to the tissue using a syringe.

85. The method of claim 80 comprising providing the composition to the tissue using a dual syringe.

86. The method of claim 80 comprising providing the composition to the tissue using a spray apparatus.

87. The method of claim 80 wherein the matrix is resorbed.

88. The method of claim 87 wherein the matrix is resorbed in about four to sixty days.

89. The method of claim 80 comprising curing the composition such that the peel strength of the matrix is about 0.08 lb/in or more.

90. The method of claim 80 wherein the matrix has a burst pressure of about 34 mmHg or greater.

91. The method of claim 90 wherein the matrix has a burst pressure of about 90 mmHg or greater.

92. The method of claim 91 wherein the matrix has a burst pressure of about 130 mmHg or greater.

93. The method of claim 80 comprising providing a composition wherein the crosslinking agent has a molecular weight in a range of about 1,000–5,000.

94. The method of claim 80 comprising providing a composition wherein the activated leaving group is an N-hydroxy imide.

95. The method of claim 94 comprising providing a composition wherein the activated leaving group is N-hydroxy succinimide.

96. The method of claim 80 further comprising mixing a first mixture and a second mixture to form the composition and applying said composition to the tissue,

wherein the first mixture includes about 20–60 wt/vol % of the protein in about 0.01–0.25 molar buffer at a pH in a range of about 8.0–11.0 and the second mixture includes about 50–800 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000–15,000.

97. The method of claim 96 wherein the crosslinking agent is of the formula

G—LM—PEG—LM—G

wherein:

—PEG— is a diradical fragment represented by the formula

$$—O—(CH_2—CH_2—O—)_a—$$

where a is an integer from 20–300;

—LM— is a diradical fragment selected from the group consisting of a carbonate diradical of the formula —C(O)—, a monoester diradical of the formula —$(CH_2)_b$C(O)— where b is an integer from 1–5, a diester diradical of the formula —C(O)—$(CH_2)_c$—C(O)— where c is an integer from 2–10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula —C(O)—O—$(CH_2)_d$—O—C(O)— where d is an integer from 2–10, and an oligomeric diradical represented by the formulas —R—C(O)—, —R—C(O)—$(CH_2)_c$—C(O)—, or —R—C(O)—O—$(CH_2)_d$—O—C(O)— where c is an integer from 2–10, d is an integer from 2–10, and R is a polymer or copolymer having 1–10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

—G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

98. The method of claim 97 wherein the protein in the first mixture is about 35–45 wt/vol % serum albumin.

99. The method of claim 98 wherein the buffer is 0.05–0.15 molar carbonate/bicarbonate buffer at a pH of about 9.0–10.5.

100. The method of claim 97 wherein the second mixture is about 50–300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000–5,000.

101. The method of claim 97 wherein the ratio of a volume of the first mixture to a volume of the second mixture is in a range of about 1:10 to about 10:1.

102. The method of claim 97 wherein —LM— is an oligomeric diradical —R—C(O)—$(CH_2)_c$—C(O)— where c is an integer from 2–10 and R is a polymer or copolymer having 1–10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone.

103. The method of claim 97 wherein —G is succinimidyl.

104. The method of claim 97 wherein the second mixture includes about 300–800 mg/ml of a crosslinking agent having a molecular weight in a range of about 5,000–15,000.

105. The method of claim 97 wherein —LM— is a diester diradical of the formula —C(O)—$(CH_2)_2$—C(O)—.

106. The method of claim 97 wherein —LM— is a diester diradical of the formula —C(O)—$(CH_2)_c$—C(O)— where c is an integer from 2–10 and where the aliphatic portion of the diradical may be saturated or unsaturated.

107. The method of claim 97 wherein —LM— is an oligomeric diradical derived from polyglycolic acid.

108. The method of claim 80 wherein the matrix binds tissue together in addition to a suture, a staple, a tape, or a bandage.

109. The method of claim 80 wherein the composition is provided to attach skin grafts.

110. The method of claim 80 wherein the composition is provided to attach adjacent layers of tissue.

111. The method of claim 80 wherein the composition is provided to position tissue flaps.

112. The method of claim 80 wherein the composition is provided to close gingival flaps.

113. A method of treating tissue comprising:

providing a composition to tissue, said composition including a serum albumin protein at about 20–60 wt/vol % and a crosslinking agent at about 50–800 mg/ml, said crosslinking agent having a polyoxyethylene chain portion and an activated leaving group which allows the crosslinking agent to react with said protein and having a molecular weight in a range of about 1000–15,000; and

curing said composition on the tissue to bond said composition to the tissue and to provide a substantive cured matrix that has a burst strength greater than about 10 mm Hg.

114. The method of claim 113 wherein said composition is cured to produce the matrix in less than about 10 minutes.

115. The method of claim 113 wherein said composition is cured to produce the matrix in less than about one minute.

116. The method of claim 113 wherein said composition is cured to produce the matrix in about ten seconds.

117. The method of claim 113 comprising providing the composition to the tissue using a syringe.

118. The method of claim 113 comprising providing the composition to the tissue using a dual syringe.

119. The method of claim 113 comprising providing the composition to the tissue using a spray apparatus.

120. The method of claim 113 wherein the matrix is resorbed.

121. The method of claim 120 wherein the matrix is resorbed in about four to sixty days.

122. The method of claim 113 comprising curing the composition such that the peel strength of the matrix is about 0.08 lb/in or more.

123. The method of claim 113 wherein the matrix has a burst pressure of about 34 mmHg or greater.

124. The method of claim 123 wherein the matrix has a burst pressure of about 90 mmHg or greater.

125. The method of claim 124 wherein the matrix has a burst pressure of about 130 mmHg or greater.

126. The method of claim 113 comprising providing a composition wherein the crosslinking agent has a molecular weight in a range of about 1,000–5,000.

127. The method of claim 114 comprising providing a composition wherein the activated leaving group is an N-hydroxy imide.

128. The method of claim 127 comprising providing a composition wherein the activated leaving group is N-hydroxy succinimide.

129. The method of claim 113 further comprising mixing a first mixture and a second mixture to form the composition and applying said composition to the tissue, wherein the first mixture includes about 20–60 wt/vol % of the protein in about 0.01–0.25 molar buffer at a pH in a range of about 8.0–11.0 and the second mixture includes about 50–800 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000–15,000.

130. The method of claim 129 wherein the crosslinking agent is of the formula

G—LM—PEG—LM—G

wherein:

—PEG— is a diradical fragment represented by the formula

$$—O—(CH_2—CH_2—O—)_a—$$

where a is an integer from 20–300;

—LM— is a diradical fragment selected from the group consisting of a carbonate diradical of the formula —C(O)—, a monoester diradical of the formula —$(CH_2)_b$C(O)— where b is an integer from 1–5, a diester diradical of the formula —C(O)—$(CH_2)_c$—C(O)— where c is an integer from 2–10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula —C(O)—O—$(CH_2)_d$—O—C(O)— where d is an integer from 2–10, and an oligomeric diradical represented by the formulas —R—C(O)—, —R—C(O)—$(CH_2)_c$—C(O)—, or —R—C(O)—O—$(CH_2)_d$—O—C(O)— where c is an integer from 2–10, d is an integer from 2–10, and R is a polymer or copolymer having 1–10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

—G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

131. The method of claim 130 wherein the protein in the first mixture is about 35–45 wt/vol % serum albumin.

132. The method of claim 131 wherein the buffer is 0.05–0.15 molar carbonate/bicarbonate buffer at a pH of about 9.0–10.5.

133. The method of claim 130 wherein the second mixture is about 50–300 mg/ml of the crosslinking agent having a molecular weight in a range of about 1,000–5,000.

134. The method of claim 130 wherein the ratio of a volume of the first mixture to a volume of the second mixture is in a range of about 1:10 to about 10:1.

135. The method of claim 130 wherein —LM— is an oligomeric diradical —R— C(O)—$(CH_2)_c$— where c is an integer from 2–10 and R is a polymer or copolymer having 1–10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone.

136. The method of claim 130 wherein —G is succinimidyl.

137. The method of claim 130 wherein the second mixture includes about 300–800 mg/ml of a crosslinking agent having a molecular weight in a range of about 5,000–15,000.

138. The method of claim 130 wherein —LM— is a diester diradical of the formula —C(O)—$(CH_2)_2$—C(O)—.

139. The method of claim 130 wherein —LM— is a diester diradical of the formula —C(O)—$(CH_2)_c$—C(O)— where c is an integer from 2–10 and where the aliphatic portion of the diradical may be saturated or unsaturated.

140. The method of claim 130 wherein —I.M— is an oligomeric diradical derived from polyglycolic acid.

141. The method of claim 113 comprising curing the composition on the tissue to seal the tissue.

142. The method of claim 141 comprising treating tissue to prevent or control a fluid leak.

143. The method of claim 142 wherein the fluid leak is a blood leak.

144. The method of claim 141 wherein the tissue includes an air leak.

145. The method of claim 144 wherein the air leak is in a pulmonary system.

146. The method of claim 113 wherein the composition is provided to tissue at a surgical site.

147. The method of claim 113 comprising curing the composition at the tissue to prevent a tissue adhesion.

148. The method of claim 113 wherein the composition is provided on a surface of an internal organ.

149. The method of claim 113 comprising curing the composition to form a matrix to bind tissue.

150. The method of claim 149 wherein the matrix binds tissue together in addition to a suture, a staple, a tape, or a bandage.

151. The method of claim 113 wherein the composition is provided to attach skin grafts.

152. The method of claim 113 wherein the composition is provided to attach adjacent layers of tissue.

153. The method of claim 113 wherein the composition is provided to position tissue flaps.

154. The method of claim 113 wherein the composition is provided to close gingival flaps.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : RE 38,158 E
DATED : June 24, 2003
INVENTOR(S) : Barrows, Thomas H.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 17,
Lines 62, 63 and 64, delete "[,]".

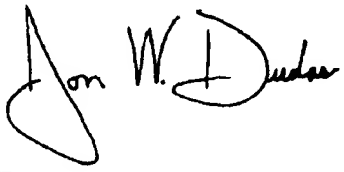
Column 18,
Line 9, delete "[and]";
Line 12, delete "[or]";
Lines 12 and 64, delete "[,]";
Lines 18, 46, 50 and 63, delete "[mixture]";
Lines 46, 50 and 54, delete "[claims]".

Column 19,
Line 1, delete "[15]";
Line 2, delete "[a]";
Lines 24, 25, 26 and 41, delete "[,]";
Line 38, delete "[and]";
Line 41, delete "[or]";

Column 25,
Line 59, "114" should be -- 113 --.

Signed and Sealed this

Sixth Day of April, 2004



JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

EXHIBIT C

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : RE 38,158 E
DATED : June 24, 2003
INVENTOR(S) : Barrows, Thomas H.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 17,
Lines 62, 63 and 64, delete "[,]".

Column 18,
Line 9, delete "[and]";
Line 12, delete "[or]";
Lines 12 and 64, delete "[,]";
Lines 18, 46, 50 and 63, delete "[mixture]";
Lines 46, 50 and 54, delete "[claims]".

Column 19,
Line 1, delete "[15]";
Line 2, delete "[a]";
Lines 24, 25, 26 and 41, delete "[,]";
Line 38, delete "[and]";
Line 41, delete "[or]";

Column 25,
Line 59, "114" should be -- 113 --.

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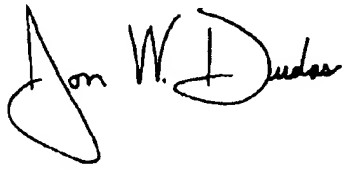

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EXHIBIT D

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5,583,114	$830.00	$0.00	03/30/00	08/281,473	12/10/96	07/27/94	04	NO	136071.01301

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PATENT NUMBER	FEE AMT	SUR-CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
RE38,158	$2,090.00	$0.00	06/10/04	09/185,732	12/10/96	07/27/94	08	NO	136071.01311

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Patent Number: RE38827

Customer Number: 21269

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PITTSBURGH PA 15219

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PATENT NUMBER	FEE AMT	SUR-CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
RE38,827	$1,955.00	$0.00	06/04/08	10/293,989	12/10/96	07/27/94	12	YES	09125-001002

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EXHIBIT E

neomend

Quality Plan

Title: Functional Testing – Surgical Sealant Kits	***Document #:*** QP-0002 ***Revision:*** C ***DCO:*** #123 ***Pages:*** 1 of 7

REDACTED

REDACTED

REDACTED

REDACTED

REDACTED

REDACTED

REDACTED
REDACTED
REDACTED
REDACTED

6.2.1.3	Albumin pH (Diluted 1:5 in 0.9% saline)	8.8 – 9.1	TM-0002	3/lot
6.2.1.4	Albumin Protein Concentration	28 – 31 gm/100 ml	AMP 10-072-CTM-200496	3/lot

REDACTED

Title: Functional Testing – Surgical Sealant Kits	*Document #:* QP-0002 *Revision:* C *DCO:* #123 *Pages:* 3 of 7

REDACTED
REDACTED
REDACTED
REDACTED
REDACTED
REDACTED

REDACTED
REDACTED

	TEST	ACCEPTANCE CRITERIA	METHOD	QUANTITY
6.2.4.1	Burst Pressure	90 mmHg minimum at 20 ± 2 minutes after rehydration of cross-linker, and Standard Deviation 25 mm Hg maximum per Sampling Plan-Attachment1	TM-0005	REDACTED

REDACTED
REDACTED

Title: Functional Testing – Surgical Sealant Kits

REDACTED
REDACTED
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REDACTED
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REDACTED

neomend
Quality Plan

Title: Functional Testing – Surgical Sealant Kits	***Document #:*** QP-0002 ***Revision:*** C ***DCO:*** #123 ***Pages:*** 7 of 7

REDACTED
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REDACTED

EXHIBIT F

NeoMend ProGel™ Pleural Air Leak Sealant

The NeoMend ProGel™ Pleural Air Leak Sealant package is provided sterile.

Caution: Federal (USA) law restricts this device to sale by or on the order of a licensed physician or properly licensed practitioner.

Information for the use of **NeoMend ProGel™** Pleural Air Leak Sealant is provided in this Labeling for Physicians and the Instructions for Use. BEFORE USING **NeoMend ProGel™** Pleural Air Leak Sealant, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY. Please direct any questions to NeoMend, Inc. 60 Technology Drive, Irvine, CA 92618 Telephone: 888-PROGEL1 or 888-776-4351, www.neomend.com

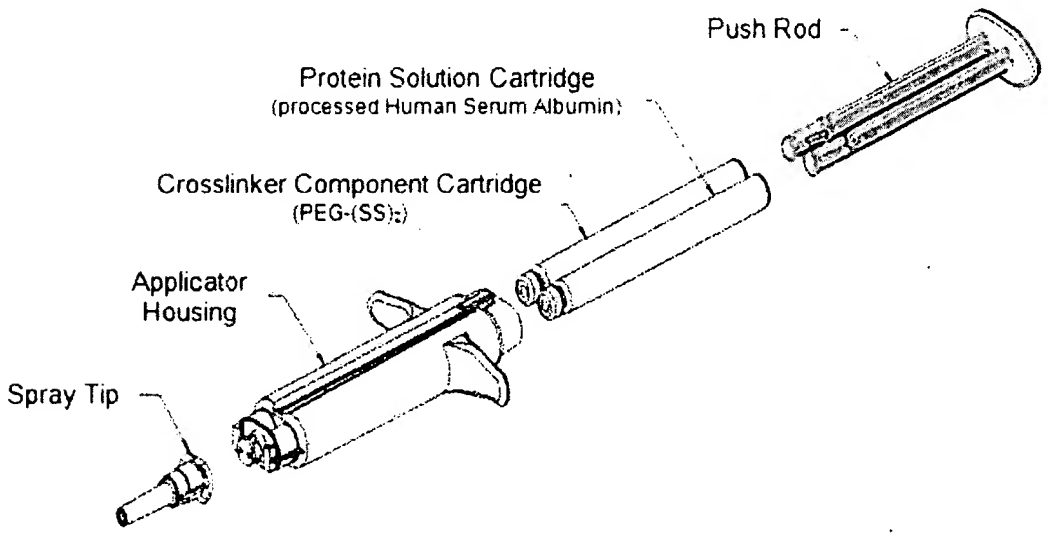
1.0 DEVICE DESCRIPTION

The NeoMend Inc. ProGel™ Pleural Air Leak Sealant ("ProGel™") is a single-use medical device that is formed as a result of mixing two components: (1) a solution of human serum albumin (HSA) and (2) a synthetic cross-linking component of polyethylene glycol (PEG) that is functionalized with succinate groups. Upon mixing a clear, flexible hydrogel is formed.

ProGel™ is supplied as a sterile, single-use, 2 - component kit which, when mixed makes a 4 ml total Sealant volume for application to visceral pleura as an adjunct to standard visceral pleural closure of visible air leaks incurred during resection of lung tissue. As ProGel™ degrades it is metabolized and cleared primarily through the kidneys. The kit includes:

- One (1) - Chemistry Kit —
  - One (1) - pre-loaded cartridge containing 2 ml of Protein solution (processed Human Serum Albumin)
  - One (1) - pre-loaded cartridge containing Polyethyleneglycol di-succinimidyl succinate ((PEG-(SS)2)) as a dried white powder.
- One (1) - Applicator Kit —
  - One (1) - 3 ml plastic syringe with 0.5 inch 26 gauge needle.
  - One (1) - 5 ml vial of USP sterile water for injection (2ml to be used to reconstitute PEG-(SS)2)
  - One (1) - Applicator assembly
  - Two (2) - Spray tips
- One (1) – Instructions for Use (Labeling)

FIGURE 1 ProGel™ PLEURAL AIR LEAK SEALANT DELIVERY SYSTEM (STERILE WATER AND SYRINGE NOT SHOWN)



2.0 INTENDED USE / INDICATIONS FOR USE

The ProGel™ Pleural Air Leak Sealant is a single use device intended for application to visceral pleura during an open thoracotomy after standard visceral pleural closure with, for example, sutures or staples, of visible air leaks (≥ 2 mm) incurred during open resection of lung parenchyma.

3.0 CONTRAINDICATIONS

- Do not use ProGel™ in patients who have a history of an allergic reaction to Human Serum Albumin or other device components.
- Do not use ProGel™ in patients who may have insufficient renal capacity for clearance of the ProGel™ polyethylene glycol load.
- Do not apply the ProGel™ on open or closed defects of main stem or lobar bronchi due to a possible increase in the incidence of broncho-pleural fistulae, including patients undergoing pneumonectomy, any sleeve resection or bronchoplasty.
- Do not apply ProGel™ on oxidized regenerated cellulose, absorbable gelatin sponges or any other surface other than visceral pleura as adherence and intended outcome may be compromised.

- Do not use more 30ml of ProGel™ per patient.

4.0 WARNINGS

ProGel™ safety and effectiveness was evaluated in 5 patients with FEV1 ≤ 40%, providing limited data about ProGel™ use in patients with FEV1 ≤ 40%. For patients with preop FEV1 ≤ or > 40%, mean (median) chest tube placement duration for patients with FEV1 ≤ 40% was 8.3 (7.0) days for ProGel™ and 5.8 (4.5) days for Control subjects; for patients with FEV1 > 40%, the mean (median) chest tube placement duration was 6.8 (5.0) days for ProGel™ and 6.2 (5.5) days for the Control cohort.

5.0 PRECAUTIONS

- The safety and effectiveness of ProGel™ has not been established in patients with the following conditions:
    - Less than 18 years of age, pregnant or nursing women.
    - Contaminated or dirty pulmonary resection cases.
    - The presence of an active infection.
    - In the presence of other sealants, hemostatic devices or products other than sutures and staples used in standard visceral pleural closure.
    - Visceral pleural air leak due to spontaneous pneumothorax, any non-resective pulmonary tissue trauma, or malignancy as well as congenital or acquired functional or anatomic defect.
    - Patients receiving the ProGel™ in more than one application session (surgery) before and / or after resorption of ProGel™ that was applied in any previous surgical session.
    - In any area or tissue other than the visceral pleural surface as indicated.
- ProGel™ use has also not been studied under any conditions other than open thoracotomy (e.g., thorascopic or endoscopic procedures).
- Inspect sterile package and seal prior to use. Do not use if sterile package or seal are damaged or open. If package and/or product integrity have been compromised (i.e., damaged package seal, or broken glass), do not use or resterilize the contents.
- The ProGel™ should be refrigerated between 2°C to 8°C (36°F to 46°F). Do not freeze. Store the ProGel™ within the recommended temperature range. Failure to do so may result in poor product performance. Do not use ProGel™ after the expiration date, as sterility or performance may be compromised.

- Do not use rehydrated cross-linker after 20 minutes, as the performance of the ProGel™ may be compromised.

- Interruption of the application for approximately 10 seconds may result in occlusion of the spray tip. If occlusion occurs, remove the spray tip, wipe the end of the applicator to remove any fluid, and attach a new spray tip (provided) onto the end of the applicator.

- The ProGel™ is intended for single use only. Do not re-sterilize or reuse any component.

- ProGel™ use with any additive (*e.g.*, antibiotics) to any component has not been studied.

- During ProGel™ application, if possible, target lung ventilation should be stopped to reduce air leakage from the targeted sites and to minimize tissue movement during ProGel™ application. If the patient needs target lung ventilation, a reduced tidal volume is recommended.

- During preparation and between sprays, wipe the applicator tip with clean, sterile gauze to remove any liquid that may have been expressed with air. Avoid mixing of components: do not wipe from one cartridge opening across to the other – wipe each opening separately.

- The unique design of the spray tip allows for ProGel™ application as a spray or as a stream (firm steady pressure on the push-rod will yield a spray, while gentle pressure will yield a stream).

- During ProGel™ application, keep the applicator tip approximately 5 cm (2 in) away from target area to avoid creating bubbles in the ProGel™ material during application. Bubbles may compromise the adherence and/or mechanical properties of the ProGel™.

- Discard unused material in accordance to standard practice for ProGel™ components.

- ProGel™ resorption time in humans has not been studied. In rats, over 50% of a ^{14}C-labeled device was excreted after 24 hours and virtually all radioactivity was recovered from rats at 14 days post-implant. The ProGel™ was also largely absent at 4 days with only isolated fragments of the ProGel™ apparent at 7 days after implantation on pigs' lungs.

- Human Serum Albumin - HSA (USP) in the ProGel™ kit is obtained from an FDA licensed supplier and the protein is derived from plasma collected from donors who have been screened and tested according to the methods specified by the FDA. These methods minimize the possibility that drawn blood will contain communicable diseases or viruses such as hepatitis and HIV.

6.0 ADVERSE EVENTS (AEs)

Table 1 presents the incidence of adverse events (AEs) reported for greater than 1% of subjects in either treatment group during a clinical study in 161 subjects randomized in a 2:1 ratio, (i.e., 103 ProGel™ and 58 Control patients).

TABLE 1. Incidence of AEs Reported by > 1% of Subjects by Treatment Group*

Preferred Term	ProGel™ N=103	Control N=58
Fever	22 (21.4%)	12 (20.7%)
Fibrillation, Atrial	12 (11.7%)	7 (12.1%)
Dyspnea	12 (11.7%)	10 (17.2%)
Constipation	11 (10.7%)	6 (10.3%)
Nausea	10 (9.7%)	7 (12.1%)
Pneumothorax	9 (7.8%)	5 (8.6%)
Confusion	8 (7.8%)	5 (8.6%)
Hypotension	8 (7.8%)	6 (10.3%)
Anemia	8 (7.8%)	6 (10.3%)
Pain	7 (6.8%)	4 (6.9%)
Subcutaneous Emphysema	7 (6.8%)	5 (8.6%)
Tachycardia	7 (6.8%)	6 (10.3%)
Death	5 (4.9%)	4 (6.9%)
Oliguria	5 (4.9%)	1 (1.7%)
Vomiting	5 (4.9%)	7 (12.1%)
Pneumonia	5 (4.9%)	7 (12.1%)
Pulmonary Infiltration	4 (3.9%)	0 (0.0%)
Chest Pain	4 (3.9%)	1 (1.7%)
Pleural Effusion	4 (3.9%)	3 (5.2%)
Urinary Retention	3 (2.9%)	0 (0.0%)
Ileus	3 (2.9%)	0 (0.0%)
Tachycardia, Supraventricular	3 (2.9%)	0 (0.0%)
Abdominal Pain	3 (2.9%)	0 (0.0%)
Arrhythmia	3 (2.9%)	0 (0.0%)
Extrasystoles	3 (2.9%)	0 (0.0%)
Coughing	3 (2.9%)	1 (1.7%)
Hypoxia	3 (2.9%)	1 (1.7%)
Renal Failure, Acute	3 (2.9%)	1 (1.7%)
Adult Respiratory Stress Syndrome	3 (2.9%)	1 (1.7%)
Hyperkalaemia	2 (1.9%)	0 (0.0%)
Hyponatraemia	2 (1.9%)	0 (0.0%)
Cardiac Arrest	2 (1.9%)	0 (0.0%)
ECG Abnormal	2 (1.9%)	0 (0.0%)
Renal Function Abnormal	2 (1.9%)	0 (0.0%)
Asthenia	2 (1.9%)	0 (0.0%)
Influenza-Like Symptoms	2 (1.9%)	0 (0.0%)

Preferred Term	ProGel™ N=103	Control N=58
Somnolence	2 (1.9%)	1 (1.7%)
Abdomen Enlarged	2 (1.9%)	1 (1.7%)
Atelectasis	2 (1.9%)	2 (3.4%)
Postoperative Wound Infection	2 (1.9%)	2 (3.4%)
Multiple Organ Failure	2 (1.9%)	1 (1.7%)
Anxiety	1 (1.0%)	1 (1.7%)
Withdrawal Syndrome	1 (1.0%)	1 (1.7%)
GI Haemorrhage	1 (1.0%)	1 (1.7%)
Hypokalaemia	1 (1.0%)	1 (1.7%)
Arrhythmia Atrial	1 (1.0%)	1 (1.7%)
Respiratory Disorder	1 (1.0%)	1 (1.7%)
Respiratory Insufficiency	1 (1.0%)	1 (1.7%)
Sepsis	1 (1.0%)	1 (1.7%)
Bronchial Obstruction	1 (1.0%)	1 (1.7%)
Infection Staphylococcal	1 (1.0%)	1 (1.7%)
Pruritus	1 (1.0%)	2 (3.4%)
Delirium	1 (1.0%)	2 (3.4%)
Hypertension	1 (1.0%)	2 (3.4%)
Angina Pectoris	1 (1.0%)	2 (3.4%)
Hemoptysis	1 (1.0%)	3 (5.2%)
Arthropathy	0 (0.0%)	1 (1.7%)
Gall Bladder Disorder	0 (0.0%)	1 (1.7%)
Cachexia	0 (0.0%)	1 (1.7%)
Dehydration	0 (0.0%)	1 (1.7%)
Non-protein Nitrogen Increased	0 (0.0%)	1 (1.7%)
Edema Dependent	0 (0.0%)	1 (1.7%)
Edema Generalized	0 (0.0%)	1 (1.7%)
Fibrillation Ventricular	0 (0.0%)	1 (1.7%)
Cardiac Failure	0 (0.0%)	1 (1.7%)
Hypoventilation	0 (0.0%)	1 (1.7%)
Thrombocytopenia	0 (0.0%)	1 (1.7%)
Allergic Reaction	0 (0.0%)	1 (1.7%)
Fatigue	0 (0.0%)	1 (1.7%)
Rigors	0 (0.0%)	1 (1.7%)
Infection, Fungal	0 (0.0%)	1 (1.7%)
Healing, Impaired	0 (0.0%)	1 (1.7%)
Cramps, Legs	0 (0.0%)	1 (1.7%)
Acidosis, Respiratory	0 (0.0%)	1 (1.7%)
Chyle, Leak	0 (0.0%)	1 (1.7%)

*There were no statistically significant differences ($p > 0.05$) in the incidence of AEs between the ProGel™ and Control groups.

ADVERSE EVENTS

Table 2 presents those AEs considered by the investigator to be possibly or probably related to the ProGel™. There were 3 subjects in the ProGel™ group with AEs that were considered by the investigator to be possibly or probably related to the device. The AEs reported were: chest pain, constipation, gastroesophageal reflux, nausea, cough, dyspnea; pneumothorax, and subcutaneous emphysema. All were reported as a single occurrence in the ProGel™ group. Two of the AEs, dyspnea and chest pain, were reported as "severe" and "serious", respectively and occurred in the same subject. All others were reported as mild or moderate.

Table 2 Incidence of Adverse Events in ProGel™ Group Considered Possibly or Probably Device - related.

Body System Preferred Term	ProGel™ (N=103)
Body as a Whole	
Chest Pain	1 (1.0%)
Gastrointestinal Systems	
Constipation	1 (1.0%)
Gastroesophageal Reflux	1 (1.0%)
Nausea	1 (1.0%)
Respiratory System	
Coughing	1 (1.0%)
Dyspnea	1 (1.0%)
Pneumothorax	1 (1.0%)
Skin and Appendages	
Subcutaneous Emphysema	1 (1.0%)

UNANTICIPATED ADVERSE DEVICE EVENT

A large, symptomatic pneumothorax that occurred in a 28 year old ProGel™-treated subject at three weeks post open pulmonary metastectomy and required chest tube placement was considered by the investigator to be an unanticipated adverse device effect due to the temporal relationship of the event with the use of the ProGel™. No other unanticipated adverse events were reported.

OTHER SERIOUS ADVERSE EVENTS

Table 3 presents a summary of other serious adverse events (SAEs). There were 5 other SAEs: 2 in the ProGel™ group and 3 in the Control group. Both of the ProGel™ SAEs were considered by the investigator probably not related to the device. All of the events resulted in extended hospital stays or rehospitalization; 4 subjects recovered from these events and 1 subject continued on dialysis.

Table 3 Other Serious Adverse Events

Subject ID	Age/Gender	Relationship To Device	Event	Outcome
ProGel™				
03-02-201	70/Female	Probably Not Related	Acute Renal Failure	Continues on Dialysis
03-01-211	70/Male	Probably Not Related	Myocardial Infarction	Recovered
Control				
01-01-204	83/Male	Not Related	Fluid/Air in Lung & GI Bleed	Recovered
02-02-206	67/Female	Probably Not Related	ARDS	Recovered
03-01-219	70/Male	Not Related	Dehydration	Recovered

PLEURAL AIR LEAK AND AIR SPACE EVENTS

The ProGel™ is a HSA – PEG polymer hydrogel applied to visceral pleura during open thoracotomy and expected to be resorbed within the first week after such application. Upon lung expansion, the ProGel™ interposes between visceral and parietal pleura. It is unknown if interpleural ProGel™ changes post-operative visceral and parietal pleura surface adhesion, changes surface healing and allows air leak sites to re-open upon ProGel™ resorption. Data demonstrated that pneumothorax occurred in 8.7% of the patients and 8.6% of the control patients. In addition ARDS occurred in 2.9% ProGel™ compared to 1.7% control patients; ProGel™ patients with ARDS died. Event incidences are in Table 4.

TABLE 4: Pleural Air Leak and Air Space Events

Pleural Air Leak and Air Space Events	ProGel™	Control
N	102	58
Pneumothorax as an adverse event	9 (8.7%)	5 (8.6%)
Acute Respiratory Distress Syndrome	3 (2.9%)	1 (1.7%)

RENAL EVENTS

ProGel™ degradation products are primarily cleared from the body by the kidneys. The incidence of Renal AEs along with individual subject data are in Table 5.

Table 5: Incidence of Adverse Events Related to Renal Function (n, %)

RENAL Adverse Events	ProGel™	Control
N, patients through 1MFU	95	53
Abnormal renal function	2 (1.9%)	0
Acute renal failure	3 (2.9%)	1 (1.7%)
Oliguria	5 (4.9%)	1 (1.7%)
Total number of renal adverse events* % patients with renal adverse events *1 ProGel™ patient was reported to have 2 events: abnormal renal function and oliguria	10 9/95 (9.5%)	2 2/53 (3.8%)

Subjects with renal function (RF) adverse events

Treatment	Adverse Event	BUN		Creatinine		ProGel™	Severity
		Pre-op	1 MFU	Pre-op	1 MFU	ml used	
ProGel™	Abnormal RF	25	26	1.1	1.8	6	Severe
ProGel™	Abnormal RF, oliguria	23	84**	0.7	1.8**	4	Severe
ProGel™	Acute renal failure	21	24	1.4	1.7	2	Severe
ProGel™	Acute renal failure*	54	14	3.8	5.0	2	Severe
ProGel™	Acute renal failure.	8	***	1.0	***	6	Severe
ProGel™	Oliguria*	13	17	1.1	1.3	4	Moderate
ProGel™	Oliguria*	33	39	1.7	2.2	8	Moderate
ProGel™	Oliguria	12	8	0.9	1.0	6	Mild
ProGel™	Oliguria	10	11	0.9	0.8	2	Mild
Control	Acute renal failure*	15	***	1.0	***	na	Severe
Control	Oliguria	12	11****	1.2	1.0****	na	Mild

*Pre-existing renal disease
**at discharge; no 1MFU as patient died
***no discharge or 1MFU as patient died
****at discharge; no 1MFU data

Data demonstrated pre-existing renal disease in 3 ProGel™ and 1 control patients who had a renal AE, and no pre-existing renal disease in 6 ProGel™ and 1 control patients who had a renal AE. Severe renal AEs occurred in 4 ProGel™ patients without pre-existing disease and 2 of those patients died. Severe renal AE occurred in 1 control device patient with pre-existing disease and that patient died.

All urinary system disorders occurrence was ProGel™: 12 (11.7%), Control: 2 (3.4%). Reasons for the difference between cohorts in the incidence of renal AEs are unclear; the potential of ProGel™ to exacerbate renal dysfunction in patients with pre-existing renal disease is unknown.

SUBJECT DEATHS

Table 6 presents a summary of subject deaths. 5/103 (4.9%) ProGel™ and 4/58 (6.9%) control subjects died during this study. None of the deaths were considered by the investigators to be device-related. Death in 2 ProGel™ and 1 control patient was associated with multi-organ failure. 1 control treated patient reported to have multi-organ failure was not reported to have died. Death in 2 of 3 ProGel™ patients with ARDS was associated with more than the mean (2.5 Units = 5ml) and median (2.0 Units = 4ml) amount of ProGel™ used in clinical study.

The single patient who received the maximum volume of ProGel™ used in this clinical trial (15 Units (30ml) was a 71 year old male who, about five days after bilateral lung volume reduction surgery, developed significant ALs that were repaired with ProGel™ application. ARDS was noted 0-6 hours Post-op ProGel™ application. The patient developed pulseless ventricular fibrillation and flutter and died on POD 2 after ProGel™ application; autopsy findings bilaterally included moderate pleural cavity adhesions on gross exam, congestion on cut lung surface, and fibrinous pleuritis microscopically.

TABLE 6. Summary of Subject Deaths

Age , Gender Preop ECOG Score , Preop FEV1 ≤ or > 40%	Day of Death	Relationship to Device	Cause of Death	Amount of ProGel™ used
ProGel™				
71/Male ECOG=4, FEV1≤ 40%	POD2	Not Related	ARDS	30 ml
82/Male ECOG=0, FEV1>40	POD28	Not Related	Pneumonia	4 ml
61/Male ECOG=1, FEV1>40	POD10	Not Related	Acute Airway Obstruction or Pulmonary Embolism	2 ml
66/Male ECOG=1, FEV1>40	POD6	Not Related	ARDS & Multisystem Failure	6 ml
65/Male ECOG=2, FEV1>40	POD22	Not Related	ARDS & Multisystem Failure	4 ml
Control				
80/Female ECOG=0/FEV1>40	POD19	Not Related	Pneumonia	N/A
70/Male ECOG=1/FEV1>40	POD22	Not Related	Atrial Fibrillation	N/A
82/Male ECOG=0/FEV1>40	POD0	Not Related	Ventricular Fibrillation	N/A
67/Male ECOG=unknown/FEV1>40	POD38	Not Related	Anoxic Brain Injury	N/A

N/A = Not Applicable

7.0 CLINICAL STUDY

7.1 STUDY OBJECTIVES

The primary study objective was to evaluate the safety and effectiveness of the use of ProGel™ Pleural Air Leak Sealant (ProGel™) as an adjunct to standard suture / staple closure of clinically significant (≥ 2 mm in size) intra-operative visceral pleural air leaks incurred during open resection of non-infected pulmonary tissue in adults.

7.2 STUDY DESIGN

The study was a prospective, "standard care alone" – controlled, 2 to 1 randomized trial conducted by 5 thoracic surgeon investigators and 5 sub-investigators at 5 centers in the US. Investigators received detailed device use training, which included animal model practice; the sub-investigators received basic bench - top training.

Qualifying patients were adults who were undergoing open thoracotomy and willing to use birth control up to 6 weeks post-surgery and who had intra-operative air leak (≥ 2mm) following surgery. Patients were excluded if they had a known hypersensitivity to human albumin, were enrolled in the National Emphysema Treatment Trial or any other study involving tissue sealants, or any other study not approved by the sponsor. Subjects were also excluded if pregnant and / or breast feeding, if they had significant clinical disease that might complicate surgery and / or post-operative recovery and in the investigator's opinion would complicate evaluation of device safety and effectiveness.

Enrolled patients were stratified according to pre-operative percent predicted FEV1 (≤40%, >40%). In preparation for open thoracotomy closure, after evaluation per standard protocol with air leak test and initial attempt to close air leaks (AL) with standard care (suture / staples), subjects with at least one clinically significant IOAL (≥ 2 mm in size), were randomized whether or not to receive ProGel™ as an adjunct for visceral pleural air leak closure. Investigators conducted an AL test by filling the chest cavity with warm saline solution or water to submerge the entire lung, simultaneously inflating the lung to 20-30 mm Hg (30-40 cm water) and looking for air bubbles, which would represent ALs. The size of each AL was estimated. Any AL ≥ 2 mm in size was considered clinically significant. If no leaks or only clinically insignificant leaks (< 2 mm in size) were observed, the subject was excluded. For enrolled subjects, the size (i.e., < 2 mm, 2-5 mm, and > 5 mm bubbles), location on the lung and source (e.g. staple line, fissure) of the bubbles coming from ALs were recorded. If a subject had more than 5 leaks, the investigator was only required to record data on the first five air leaks. Up to three attempts to seal AL with the ProGel™ were permitted.

Follow-up through 30 days post-operatively, included evaluation of chest x-rays, chest tube air leak, chest tube drainage, laboratory values, and AEs, as well as time to chest tube removal and patient discharge.

Chest tube management was pre-specified as follows:
The chest tube will be placed on suction (20-25 cm H20) for the first 24 hours. After 24 hours, if there is no air leak, a switch to water seal will be made. If there is still an air leak after 24 hours the switch will be at the discretion of the surgeon; a record of what was done will be noted. The chest tube will be removed when:

1. There is no more air leakage following the switch to water seal,
2. The lung has expanded sufficiently and/or there is no significant increase in the size of a pneumothorax, in the investigators opinion, that would prevent discontinuation, and
3. Drainage has reduced to < 5 cc/kg/ 24 hours or, 2.5 cc/kg/12 hours.

As to Heimlich valve use, the protocol stated that 'occasionally the attending physician will decide to discharge a subject, who still has an air leak, with a Heimlich valve. When this occurs, the subject will be asked to return on a weekly basis until the tube is removed. The date the air leak ceased will be the day the tube is removed.

7.2.2 STUDY ENDPOINTS

The primary endpoint for ProGel™ effectiveness was the percent of patients without post-operative air leak (POAL) through one month post-operatively or the duration of hospitalization, whichever is longer.

Secondary effectiveness endpoints were:

1. The proportion of intra-operative air leaks (IOAL) in each group that were sealed or reduced, as demonstrated by the air leak (AL) test, prior to the completion of lung surgery.
2. The proportion of subjects in each group who were free of air leaks immediately following surgery as measured by the presence of air leaks from the chest tube (CT) at the first post-operative time point once the subject was in the recovery room (RR).
3. The duration of post-operative air leaks measured from the time of surgery until the air leak sealed. For patients discharged with a Heimlich Valve (HV) for out-patient management of ongoing air leak, air leak duration was the number of days elapsed from surgery until the subject returned to the clinic with no evidence of an air leak.
4. The duration of chest tube placement. This endpoint included the time that the Heimlich Valve was in place.
5. The duration of hospitalization: post - operative hospital days (POD).

Safety was evaluated by assessment of AEs through 30 days post-operatively and changes in the humoral and cellular responses to the ProGel™ measured pre- and post-surgery.

7.3 SUBJECT ACCOUNTING

A total of 275 subjects were consented and enrolled and 161 subjects were randomized intra-operatively. Of the 161 randomized subjects (i.e., 103 ProGel™ and 58 Control), 148 subjects completed the study. Of the 13 subjects who did not complete the study (i.e., 1 month follow-up information was not available), 9 died, 1 had a post-ProGel™ lung transplant, 1 had a post-ProGel™ lobectomy of the treated lung, and 2 subjects were lost to follow-up. The per-treatment-distribution of these subjects was similar across groups, with 8/103 (7.8%) in the ProGel™ and 5/58 (8.6%) in the Control groups.

7.4 DEMOGRAPHICS

The demographics of the subjects enrolled in the study are presented below in Table 7.

Table 7 Patient Demographics

.		ProGel™	Control
N		103	58
Gender:	Male	66 (64.1%)	36 (62.1%)
	Female	37 (35.9%)	22 (37.9%)
Age, years:	Mean	63.6	65.9
	SD	13.6	11.1
Percent predicted FEV1:	≤ 40%	5 (4.9%)	4 (6.9%)
	> 40%	93 (90.3%	53 (91.4%)
	Missing	5 (4.9%)	1 (1.7%)
Immunosuppression:	No	98 (95.1%)	55 (94.8%)
	Yes	5 (4.9%)	3 (5.2%)
Diabetes:	No	90 (87.4%)	51 (87.9%)
	Yes	13 (12.6%)	7 (12.1%)
COPD:	No	68 (66.0%)	42 (72.4%)
	Yes	35 (34.0%)	16 (27.6%)
Previous Thoracic Surgery:	No	88 (85.4%)	48 (82.8%)
	Yes	15 (14.6%)	10 (17.2%)
Radiation Exposure – Chest:	No	94 (91.3%)	53 (91.4%)
	Yes	9 (8.7%)	5 (8.6%)
Chemotherapy:	No	94 (91.3%)	56 (96.6%)
	Yes	9 (8.7%)	2 (3.4%)
Steroid Use:	No	99 (96.1%)	55 (94.8%)
	Yes	4 (3.9%)	3 (5.2%)
Smoking:	Never	20 (19.4%)	11 (19.0%)
	Current	18 (17.5%)	11 (19.0%)
	Former	65 (63.1%)	36 (62.1%)
Pack Years			
N		78	46
Mean ± SD		59.8 ± 36.0	47.6 ± 27.3
Median		50.0	40.5
Minimum		1	1
Maximum		175	120
Hypertension		40 (38.8%)	26 (44.8%)
Immunosuppression		5 (4.9%)	3 (5.2%)
History of Myocardial Infarction		11 (10.7%)	10 (17.2%)
Coronary Artery Disease		21 (20.4%)	19 (32.8%)
Renal Disease		13 (12.6%)	5 (8.6%)
History of Neurological Event		7 (6.8%)	5 (8.6%)
Diabetes		13 (12.6%)	7 (12.1%)
Congestive Heart Failure		4 (3.9%)	3 (5.2%)
Chronic Obstructive Pulmonary Disease		35 (34.0%)	16 (27.6%)
Previous Thoracic Surgery		15 (14.6%)	10 (17.2%)
Radiation Exposure-Chest		9 (8.7%)	5 (8.6%)
Chemotherapy		9 (8.7%)	2 (3.4%)

	ProGel™	Control
N	103	58
Steroid Use	4 (3.9%)	3 (5.2%)
Recent Weight Loss	13 (12.6%)	9 (15.5%)
Alcohol Dependency		
No	82 (79.6%)	44 (75.9%)
Current	6 (5.8%)	7 (12.1%)
Past	15 (14.6%)	7 (12.1%)
Prior Cancer	36 (35.0%)	25 (43.1%)
ECOG Score		
0 = Fully active	72 (69.9%)	38 (65.5%)
1 = Ambulatory	23 (22.3%)	18 (31.0%)
2 = In bed <50%	2 (1.9%)	0 (0.0%)
3 = In bed >50%	0 (0%)	0 (0%)
4 = Bedridden	1 (1.0%)	0 (0.0%)
Missing	5 (4.9%)	2 (3.4%)

None of the differences between ProGel™ and Control groups for the reported demographic and risk variables was found to be statistically significant per Wilcoxon Rank Sum Test. The enrollment of patients with percent predicted FEV1 $\leq$ 40% was less than 6% of each cohort limiting clinical assessment of outcomes for this cohort. There were no clinically notable or statistically significant differences in pre-operative pulmonary function test results.

PRIMARY DIAGNOSIS AND PROCEDURE VARIABLES

Table 8 presents a summary of primary diagnoses, type of surgery, surgical approach, extent of lymphadenectomy, intra-operative air leak (IOAL) distribution and extent of pleural adhesions.

Table 8: Primary Diagnosis and Procedure Variables

	ProGel™	Control
N	103	58
Primary Diagnosis, p = 0.620		
Primary Tumor	70 (68.0%)	42 (72.4%)
Metastatic Tumor	19 (18.4%)	8 (13.8%)
Benign Tumor	6 (5.8%)	3 (5.2%)
COPD/Bronchitis/Emphysema	3 (2.9%)	0 (0.0%)
Other	5 (4.9%)	5 (8.6%)
Type of Surgery, p = 0.883		
Bilobectomy	4 (3.9%)	1 (1.7%)
Lobectomy	55 (53.4%)	34 (58.6%)
Segmentectomy	5 (4.9%)	4 (6.9%)
Single Wedge	12 (11.7%)	7 (12.1%)
Multiple Wedge	8 (7.8%)	2 (3.4%)
Lobectomy with Wedge(s)	10 (9.7%)	5 (8.6%)
Lobectomy/Segment./Other	5 (4.9%)	2 (3.4%)
Lung Volume Reduction	1 (1.0%)	1 (1.7%)
Other	3 (2.9%)	2 (3.4%)

Surgical Approach, p = 0.269		
Median Sternotomy	1 (1.0%)	1 (1.7%)
Posterolateral Thoracotomy	85 (82.5%)	45 (77.6%)
Anterolateral Thoracotomy	3 (2.9%)	6 (10.3%)
Mini-thoracotomy	13 (12.6%)	6 (10.3%)
Other	1 (1.0%)	0 (0.0%)
Lymphadenectomy, p = 0.201		
Not done	30 (29.1%)	11 (19.3%)
Partial	30 (29.1%)	14 (24.6%)
Complete	43 (41.7%)	32 (56.1%)
Pleural Adhesions, p = 0.597		
Missing	1 (1.0%)	1 (1.7%)
No	49 (47.6%)	27 (46.6%)
Yes:	53 (51.5%)	30 (51.7%)
Unspecified	3 (5.7%)	1 (3.3%)
Minimal	28 (52.8%)	14 (46.7%)
Extensive	22 (41.5%)	15 (50.0%)
IOAL prior to closure actual distribution, p = 0.0051		
1	33 (32.0%)	30 (51.7%)
2	46 (44.7%)	14 (24.1%)
3	16 (15.5%)	6 (10.3%)
4	2 (1.9%)	5 (8.6%)
5	4 (3.9%)	0 (0.0%)
>5	2 (1.9%)	3 (5.2%)
IOAL statistical distribution, p= 0.134		
Mean	3.0	2.0
SD	9.7	1.4
Median	2.0	1.0
Minimum	1	1
Maximum	100	7

The most frequent type of surgery was lobectomy for both groups. In both the ProGel™ and Control groups, the posterolateral thoracotomy was the most frequently used surgical approach for open thoracotomy. Intra-operative characteristics were similar between the ProGel™ and Control groups for the individual parameters evaluated. Data indicates that the baseline distribution of IOAL was statistically different between treatment groups (p=0.0051); the mean and median were not. Other variables were not statistically different as powered in this study.

Number of ProGel™ Applications:

A 2ml of ProGel™ was expected to cover a 20 cm^2 (3 in^2) surface area with 1 mm thickness of ProGel™, which was expected to be sufficient to treat an average clinically significant visceral pleural AL. Up to three applications of ProGel™ were allowed per individual air leak. Table 9 reports the actual number of ProGel™ applications as well as the number of 2ml ProGel™ units used per patient.

TABLE 9. Volume of ProGel™ Pleural Air Leak Sealant Use

Volume of ProGel™ Used per Patient (ml)	
2	29 (28.2%)
4	37 (35.9%)
6	22 (21.4%)
8	7 (6.8%)
10	4 (3.9%)
12	2 (1.9%)
18	1 (1.0%)
30	1 (1.0%)
Mean ±SD	4.8 ±3.6
Median	4.0
Minimum	2
Maximum	30
Number of ProGel™ Applications Per AL	**ProGel™ - N (%)**
One	125 (59.5)
Two	70 (33.3)
Three	9 (4.3)
Missing/Other	6 (2.9)
Time (minutes) of Application / Unit	
Mean ±SD	3.3 ±4.7
Median	2.0
Minimum	1
Maximum	
Total Application Time (minutes)	
Mean ±SD	7.9 ±8.4
Median	6.0
Minimum	1
Maximum	63

Table 10 provides additional information on patient surgeries.

TABLE 10 Other Operative Details

Treatment		*ProGel™*	*Control*
No. of Chest Tubes	*1*	*19 (18.4%)*	*7 (12.1%)*
	2	*83 (80.6%)*	*48 (82.8%)*
	≥3	*1 (1.0%)*	*3 (5.2%)*
Time in OR (min)	*N*	*102*	*58*
	Mean ± SD	*226.7 ± 61.2*	*236.8 ± 61.5*
	Median	*225.5*	*225.5*
	Minimum	*115*	*145*
	Maximum	*455*	*430*
Time to Skin Closure	*N*	*91*	*50*
(min)	*Mean ± SD*	*156.8 ± 54.9*	*165.0 ± 62.6*
	Median	*151.0*	*143.5*
	Minimum	*52*	*81*
	Maximum	*355*	*387*

[1] Percents based on the number of subjects who had pleural adhesions rated at the time of surgery.

7.8 EFFECTIVENESS

Primary Effectiveness Outcome

Percentage of subjects who remained air leak-free through the 1 MFU visit is presented in Table 11.

TABLE 11 Primary Endpoint Results

Air Leak Status Through 1MFU Visit	ProGel™ N (%)	Control N (%)	P-value[a]
No POAL	36 (35.0%)	8 (13.8%)	0.005
With POAL	67 (65.0%)	50 (86.2%)	

[a]Logistic regression analysis comparing ProGel™ and Control groups for the primary endpoint analysis.

As to stratification for pre-op FEV1 ≤ or > 40%, all 5 ProGel™ and 4 Control patients with FEV1 ≤ 40% had POAL; whereas 59/93 (63.4%) ProGel™ and 45/53(84.9%) Control patients with FEV1 > 40% had POAL.

Secondary Effectiveness Outcomes

- Proportion of intra-operative air leaks (IOAL) in each group that were sealed or reduced, as demonstrated by the air leak (AL) test, prior to the completion of lung surgery is presented in Table 12. Of the 210 ALs tracked in the ProGel™ group, 76.7% were sealed after the application of ProGel™ compared with 15.7% of the 108 ALs in the Control group. IOALs

were sealed in 70.9% of the ProGel™ and 10.3% of the Control subjects following the final AL test.

TABLE 12. IOAL Closure Summary

Parameter	Response	ProGel™ N (%)	Control N (%)	P-value[a]
Sealed IOAL/Individual AL	No IOAL	161 (76.7%)	17 (15.7%)	< 0.001
	<2 mm	23 (11.0%)	13 (12.0%)	
	2-5 mm	21(10.0%)	60 (55.6%)	
	>5 mm	5 (2.4%)	17 (15.7%)	
	Missing	0 (0.0%)	1 (0.9%)	
Sealed IOAL/Subject	No IOALs	73 (70.9%)	6 (10.3%)	< 0.001
	With IOALs	30 (29.1%)	51 (87.9%)	
	Missing	0 (0.0%)	1 (1.7%)	

[a]p-value associated with Fisher's Exact Test for categorical data.

- Proportion of subjects in each group who were free of air leaks immediately following surgery as measured by the presence of air leaks from the chest tube (CT) at the first post-operative time point once the subject was in the recovery room (RR) is presented in Table 13. After surgery, subjects were transferred to the recovery room where chest tubes (CTs) were placed on suction and the subjects' air leakage was determined by observing air bubbles in the CT drainage system. A statistically significant number of ProGel™ subjects were air leak-free in recovery room compared to Control subjects. No ALs were observed in the recovery room in 54% of the ProGel™ and 33% of the Control subjects.

TABLE 13. Summary of POALs in the Recovery Room

Observation Period	Response	ProGel™ N (%)	Control N (%)	P-value[a]
Recovery Room	No AL	56 (54.4%)	19 (32.8%)	0.002
	Occasional Infrequent Bubbles	30 (29.1%)	20 (34.5%)	
	Frequent Bubbles	7 (6.8%)	16 (27.6%)	
	Continuous Bubbles	8 (7.8%)	3 (5.2%)	
	Missing	2 (1.9%)	0 (0.0%)	

[a]P-value associated with Fisher's Exact Test of categorical data.

- Duration of post-operative air leaks measured from the time of surgery until the air leak sealed. For patients discharged with a Heimlich Valve (HV) for out-patient management of an ongoing air leak, air leak duration was the number of days elapsed from surgery until the subject returned to the clinic with no evidence of an air leak. Duration of POAL was defined as the first postoperative day (POD) on which the AL was noted. Time to no air leak is presented in Table 14.

Table 14: Duration of Post-Operative Air Leaks*

	Post-op		
Duration POAL	ProGel™	Control	
N (%)			
Missing	2 (1.9%)	2 (3.4%)	
0-2 days	54 (52.4%)	29 (50.0%)	
3-4 days	18 (17.5%)	14 (24.1%)	
5-6 days	7 (6.8%)	6 (10.3%)	
7-9 days	6 (5.8%)	1 (1.7%)	
10-11 days	3 (2.9%)	3 (5.2%)	
> 11 days	13 (12.6%)	3 (5.2%)	
Mean	4.7	3.6	
SD	6.8	3.9	
Median	2.0	2.0	
Minimum	0.5	0.5	
Maximum	42	22	
N	101	56	

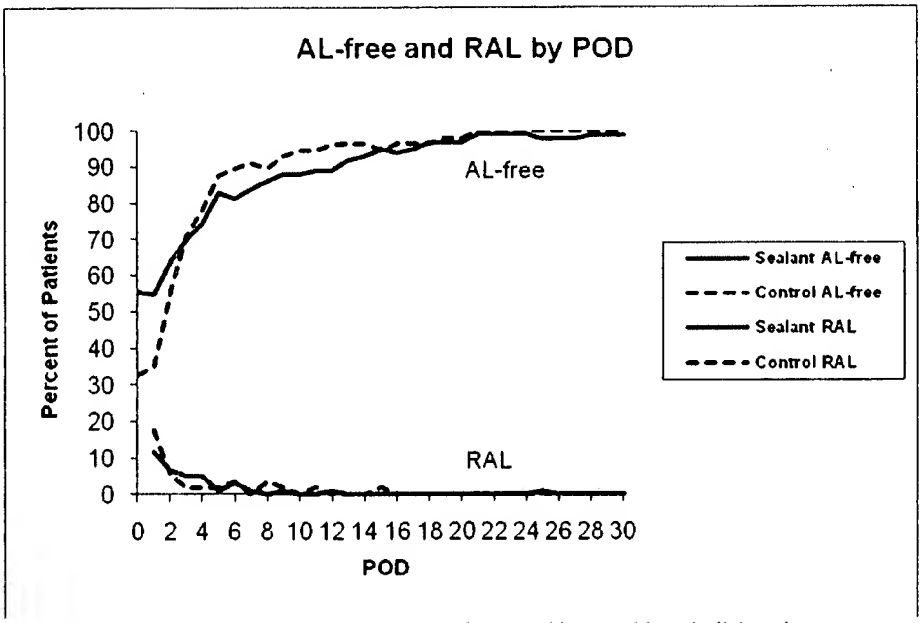
*Differences were not statistically significant as determined by a Wilcoxon Rank Sum Test comparing ProGel™ and Control groups based on all available data (N=157).

Data demonstrate that overall the mean duration of Post-Operative Air Leaks was 1.1 days longer for the ProGel™ cohort than the control cohort, with no difference in the median duration (2 days in each cohort). Data also indicate that while 2.4% more ProGel™ patients had no air leak at 0-2 days, 10.1% more control patients had no air leak at 3-6 days, and that 7.4% more ProGel™ patients' air leak continued through more than 11 days.

It is clinically notable that ten (10%) subjects in the ProGel™ group and one (2%) subject in the Control group were discharged from the hospital with a Heimlich valve [the difference was not statistically significant as powered in this study]. Since patients discharged with a HV valve were re-evaluated weekly rather than daily, patient discharge from the hospital with a HV confounded determination of the true duration of post-operative air-leaks, which may in part explain the higher proportion of ProGel™ patients with air leak that continues through more than 11 days.

As to stratification for preop FEV1 $\leq$ or > 40%, mean (median) air leak duration for patients with FEV1 $\leq$ 40% was 6.3 (4.0) days for ProGel™ and 4.3 (3.0) days for Control subjects; for patients with FEV1 > 40% the mean (median) air leak duration was 4.7 (2.0) days for ProGel™ and 3.6 (2.0) days for the Control cohorts.

Air-leak Free and Recurrence of Air Leak by Post-operative Days (POD)



Note: For all patients (n = 161), including those discharged home with Heimlich Valve.

Recurrence of air leak (RAL) is defined as chest tube documented air leak following one or more air-leak free days. One ProGel™ patient experienced a late pneumothorax on POD25 was also counted as having a recurrence of air leak. Overall, data demonstrates that the duration of POALs was comparable for both treatment groups with a majority of POALs lasting less than three days: median duration was two days in both groups. For each post-operative day, patients were excluded from the analysis if they were dead, lost to follow-up, had no air-leak assessment, received lung transplant, or completed 1MFU. Patients who were discharged with a Heimlich valve were counted as having AL on the post-operative days between the date of discharge and the date of chest tube removal.

- **Duration of Chest Tube Placement**

Table 15 presents a summary of the duration of CT placement in number of postoperative days. The duration of chest tube placement was comparable for both treatment groups. The median duration of CT placement for both groups was five days.

TABLE 15. Duration of CT Placement[a]

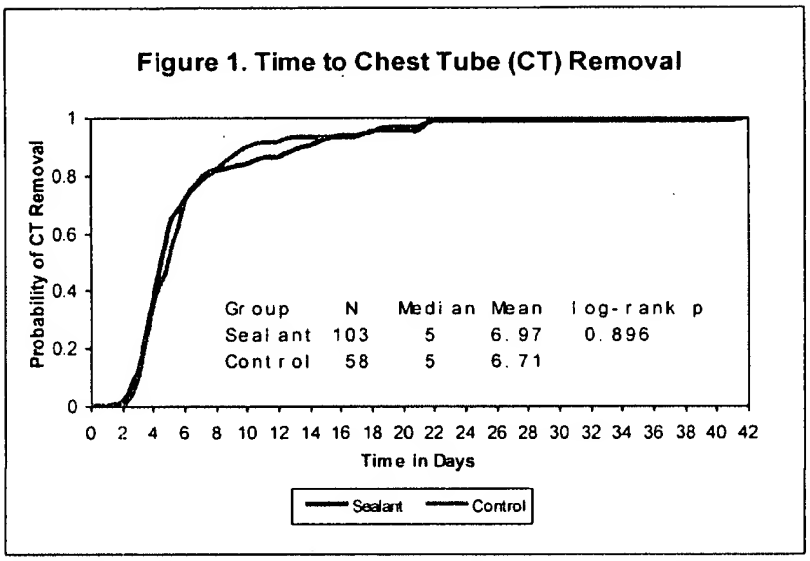
CT Duration	ProGel™ N (%)	Control N (%)
N	103	58
Missing[b]	3 (2.9%)	3 (5.2%)
N	100	55
0-2 days	2 (1.9%)	0 (0.0%)
3-4 days	34 (33.0%)	19 (32.8%)
5-6 days	37 (35.9%)	21 (36.2%)
7-9 days	11 (10.7%)	9 (15.5%)
10-11 days	3 (2.9%)	3(5.2%)
> 11 days	13 (12.6%)	3 (5.2%)
Mean	6.8	6.2
SD	5.5	3.5
Median	5.0	5.0
Minimum	2	3
Maximum	42	22

[a] Differences were not statistically significant as determined by a Wilcoxon Rank Sum Test comparing ProGel™ and Control groups based on all available data (N=155).

[b] "Missing" subjects were either censored (incomplete, i.e., entered the study late and didn't have chance to complete the whole study, lost-to-follow-up, or other causes). The time-to-event survival analyses included all subjects into the analyses and used all subject information up to the time they were censored.

Consistent results were observed using a survival analysis, which included all randomized patients (N=161) and treated patients with missing time of CT removal as censored observations. The results of the survival analysis are shown in Figure 1.

As to stratification for preop FEV1 $\leq$ or > 40%, mean (median) chest tube placement duration for patients with FEV1 $\leq$ 40% was 8.3 (7.0) days for ProGel™ and 5.8 (4.5) days for Control subjects; for patients with FEV1 > 40%, the mean (median) chest tube placement duration was 6.8 (5.0) days for ProGel™ and 6.2 (5.5) days for the Control cohorts.



Note: For all patients (n = 161), including those discharged home with Heimlich Valve

- **Duration of hospitalization: post - operative hospital days (POD)**

Table 16 presents the length of hospital stay in days.

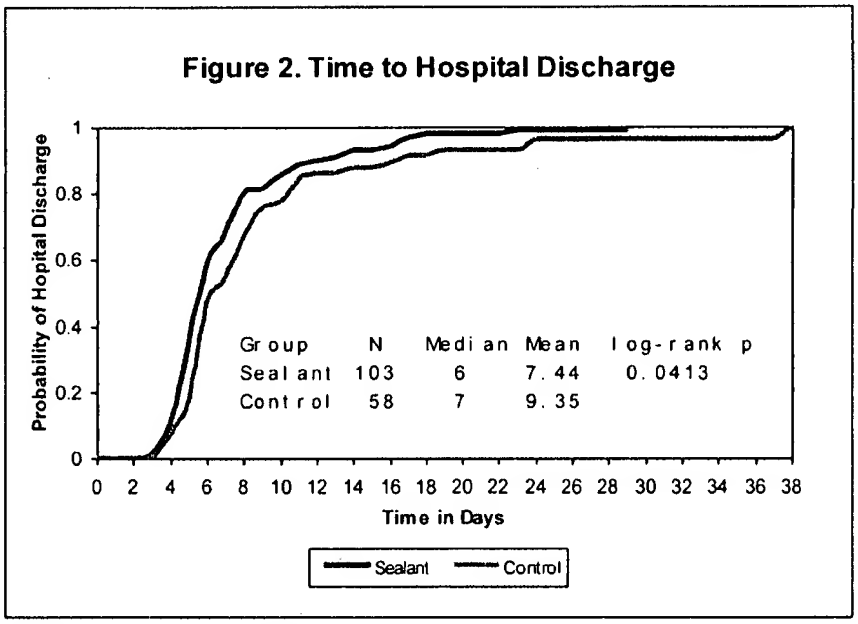
Table 16 Duration of hospitalization POD

Hospital stay, days	ProGel™ N (%)	Control N (%)	P
N	103	58	
Missing[b]	5 (4.9%)	3 (5.2%)	0.0413
N	98	55	
3-4 days	11 (10.7%)	4 (6.9%)	
5-6 days	49 (47.6%)	23 (39.7%)	
7-9 days	22 (21.4%)	16 (27.6%)	
10-11 days	7 (6.8%)	5 (8.6%)	
> 11 days	9 (8.7%)	7 (12.1%)	
Mean	7.44	9.35	
SD	3.4	5.6	
Median	6.0	7.0	
Minimum	3	4	
Maximum	23	38	

[a]P-value associated with Wilcoxon Rank Sum Test comparing ProGel™ and Control groups based on all available data (N-155)

[b] "Missing" subjects were either censored (incomplete, i.e., entered the study late and didn't have chance to complete the whole study, lost-to-follow-up, or other causes). The time-to-event survival analyses included all subjects into the analyses and used all subject information up to the time they censored.

Consistent results were observed using a survival analysis, which included all randomized patients (N=161) and treated patients with missing time of hospital discharge as censored observations. The results of the survival analysis are shown in Figure 2.



Note: For all patients (n = 161), including those discharged home with Heimlich Valve

7.9 OTHER SAFETY ASSESSMENT

HUMORAL AND CELL-MEDIATED IMMUNE RESPONSE

Both pre- and post-operative serum samples were obtained from 71/103 (69%) ProGel™ and 37/58 (64%) Control subjects. Seventy (70) of the ProGel™ and 36 of the Control subjects showed no immune reaction to the ProGel™. One (1) subject in each group had pre-operative and post-operative serum levels consistent with the presence of ProGel™ antibodies prior to device exposure.

The response of peripheral blood mononuclear cells to various concentrations of mitogens (i.e., Con A, PHA, and PWM), recall antigens *(Candida* and Tetanus), and ProGel™ was tested by mixed lymphocyte proliferative assay (LPA) in pre- and postoperative whole blood samples. Mitogen analyses were compared in pre- and postoperative samples of 59 ProGel™ and 34 Control subjects and recall antigen and ProGel™ analyses were performed in 69 ProGel™ and 32 Control subjects. No clinically significant differences were observed in the pre and postoperative blood samples for either Control or ProGel™ subjects.

8.0 PATIENT COUNSELING INFORMATION

The physician should discuss the following with patients potentially receiving ProGel™:

- The Indication for ProGel™ Use
- The risk/benefit issues associated with ProGel™ use.
- The presence of HSA prepared from pooled human plasma donors in the final product. Use of this product presents some risk of transmitting infectious agents. While this risk is deemed remote, it cannot be totally excluded. This also applies to pathogens that are as yet unknown.

The Human Serum Albumin (HSA-USP) used to manufacture the ProGel™ is obtained from a U.S. Food and Drug Administration (FDA) licensed supplier and is derived from plasma collected from donors who have been previously screened and tested according to the methods specified by the FDA. These methods are designed to minimize the possibility that blood drawn from donors will contain communicable diseases or viruses such as hepatitis and HIV.

9.0 INSTRUCTIONS FOR USE

The ProGel™ Pleural Air Leak Sealant is a single use device intended for application to visceral pleura during an open thoracotomy after standard visceral pleural closure with, for example, sutures or staples, of visible air leaks (≥ 2 mm) incurred during open resection of lung parenchyma.

- **ASSESS AIR LEAKS AFTER STANDARD SUTURE / STAPLE CLOSURE**

After applying standard suture / staple closure methods to seal air leaks, repeat the underwater air leak test to assess for persistent air leaks from the visceral pleura. If visible air leaks (≥ 2 mm) from the visceral pleura are observed, consider applying the ProGel™. During clinical study the size of each AL was estimated. Any AL ≥ 2 mm in size was considered clinically significant.

If a patient is candidate for ProGel™ use, perform the following steps:

- **INSPECT PROGEL™ PACKAGE**

The ProGel™ kit consists of two sealed, sterile packages. Contents:

- One (1) - Chemistry Kit — e-beam sterilized
  - One (1) - pre-loaded cartridge containing 2 ml of processed Human Serum Albumin
  - One (1) - pre-loaded cartridge containing 260 mg of Polyethyleneglycol di-succinimidyl succinate ((PEG-(SS)2)) as a dried white powder.
- One (1) - Applicator Kit — ethylene oxide sterilized
  - One (1) - 3 ml plastic syringe with 0.5 inch 26 gauge needle.

- One (1) - 5 ml vial of USP sterile water for injection (Used for reconstitution of the PEG-(SS)2)
- One (1) - Applicator assembly
- Two (2) - Spray tips

- One (1) – Instructions For Use insert (Labeling)

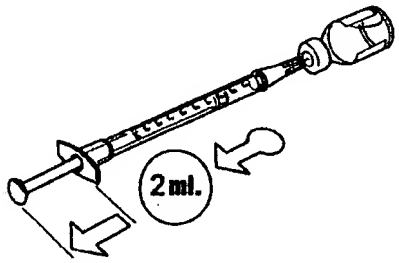
Inspect the packages before opening. Do not use ProGel™ after the "Expiration" date, because sterility or performance may be compromised. If package and/or product integrity have been compromised (i.e., damaged package seal, or broken glass), do not use or resterilize the contents. Refer to other 'precautions' as listed in the beginning of this labeling.

- **PREPARE PROGEL™**

Using aseptic technique, open the sterile package and pass the following contents into the sterile field. Cartridges may be assembled into the delivery system in any order. Load each cartridge as follows.

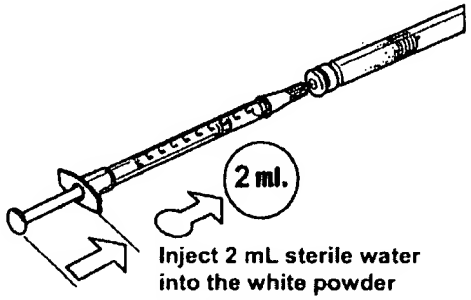
- One (1) - pre-loaded cartridge containing 2 ml of processed Human Serum Albumin
  - Note: This cartridge can be identified by examining the differences between the two contents. The Human Serum Albumin cartridge is in liquid form and has a slight yellow tint to the solution. The Crosslinker cartridge containing the Polyethyleneglycol di-succinimidyl succinate ((PEG-(SS)2)) is in the form of a white powder.
- One (1) - pre-loaded cartridge containing 260 mg of Polyethyleneglycol di-succinimidyl succinate ((PEG-(SS)2)) as a dried white powder.
  - Note: This cartridge can be identified by examining the differences between the two contents. The Crosslinker cartridge containing the Polyethyleneglycol di-succinimidyl succinate ((PEG-(SS)2)) is in the form of a white powder. The Human Serum Albumin cartridge is in liquid form and has a slight yellow tint to the solution. .
- One (1) - 3 ml plastic syringe with 0.5 inch 26 gauge needle.
- One (1) - 5 ml vial of USP sterile water for injection (Used for reconstitution of the PEG-(SS)2)
- One (1) - Applicator assembly

Step 1. Using the 3 ml syringe, draw 2 ml of sterile water into the syringe and express all air in the syringe (syringe and sterile water are provided in the Applicator Kit).



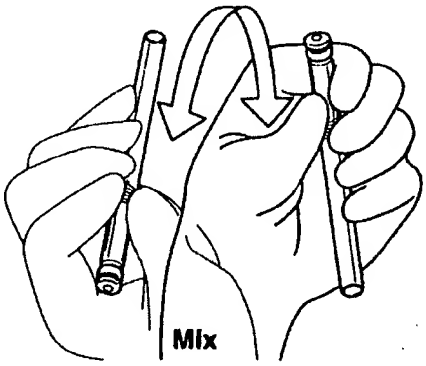
Draw 2 mL sterile water

Step 2. Inject the 2 ml of sterile water into the cartridge containing the cross-linker, (white powder cartridge provided in the Chemistry Kit). Note: The Human Serum Albumin cartridge contains a yellow liquid. Water is to only be injected in to the cross-linker (white powder) cartridge.

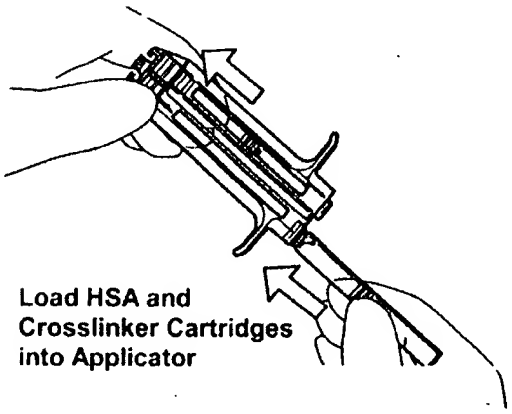


Inject 2 mL sterile water into the white powder Crosslinker Cartridge

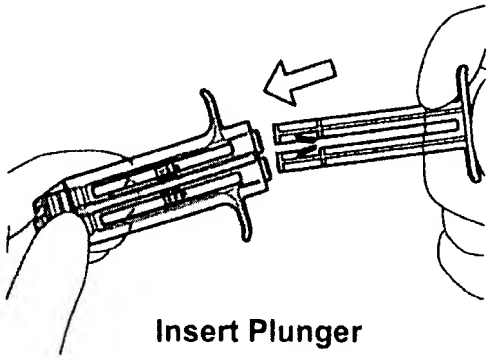
Step 3. Mix water and the cross-linker in the cartridge by gently rocking the cartridge from end to end (generally 1-2 minutes) until the solution contains no undissolved powder. When all powder is dissolved, the cross-linker is ready for use. Note: The ProGel™ should be used within 20 minutes after dissolving the cross-linker in water.



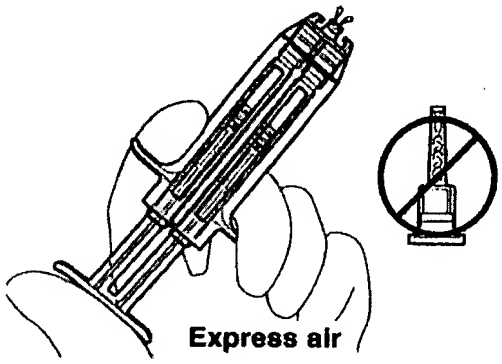
Step 4. Without the spray tip attached, point the applicator injection tip up and load each cartridge into the twin-chambered applicator housing. Gently press the cartridges to seat them into place.



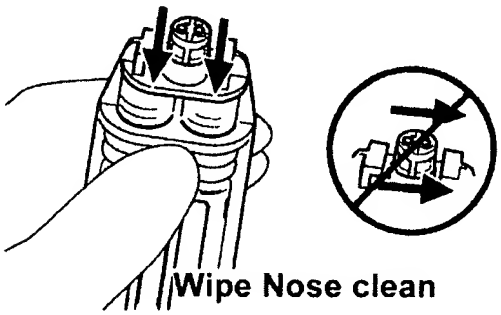
Step 5. Insert the push rod into the openings in the rear of the cartridges.



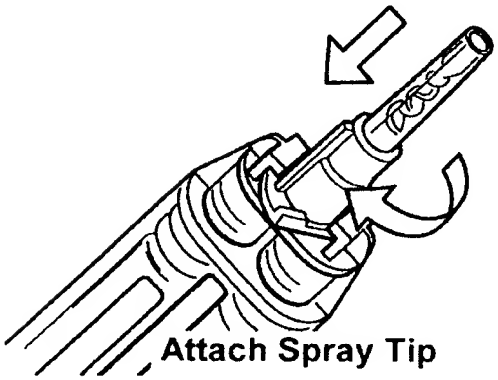
Step 6. With the tip of the applicator pointed upward, briskly flick the applicator to free any air bubbles. Express the air by gently but firmly pushing up on the push-rod until the stoppers in each cartridge are aligned with one another. Take care to express as little fluid as possible during this process.



Step 7. Wipe the applicator tip with clean, sterile gauze to remove any liquid that may have been expressed with the air. Avoid mixing of components: do not wipe from one cartridge opening across to the other – wipe each opening separately.



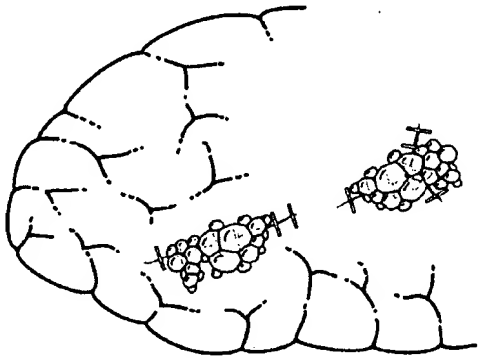
Step 8. Place a spray tip on the tip of the applicator and rotate the spray tip clockwise 1/4 turn until locked.



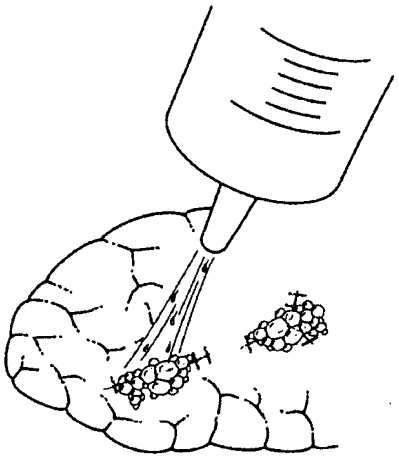
Step 9. The ProGel™ is ready for application..

- **APPLY PROGEL™**

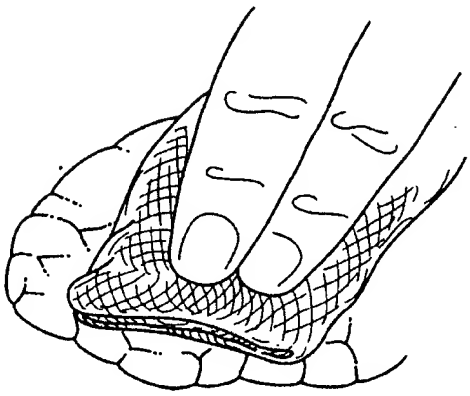
Step 10. During preparation for open thoracotomy closure after pulmonary tissue resection, after applying standard suture / staple closure methods to seal identified air leaks, repeat the submersion air leak test to assess for persistent visible air leaks (≥ 2 mm) from the visceral pleura. If visible air leaks from the visceral pleura, note AL location and consider applying the ProGel™.



Step 11. Rinse the visceral pleural surface to be treated with sterile saline to remove any pooled blood or blood clots with irrigation and/or suction.

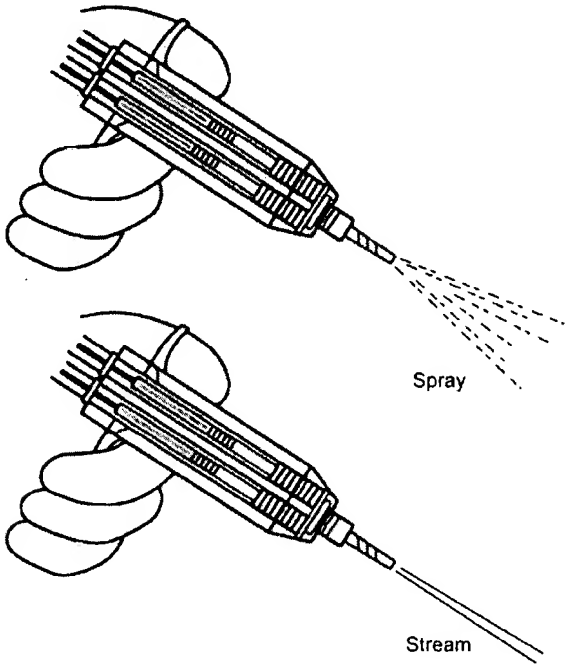


Step 12. Blot the target tissue area with a sponge or gauze to remove excess moisture.



Step 13. Ventilation to the affected area should be stopped. If ventilation needs to be maintained, reducing the tidal volume is recommended to minimize air leakage and lung movement during application of the sealant.

Step 14. The unique design of the spray tip allows for ProGel™ application as a spray or as a stream. Firm steady pressure on the push-rod will yield a spray, while gentle pressure will yield a stream.

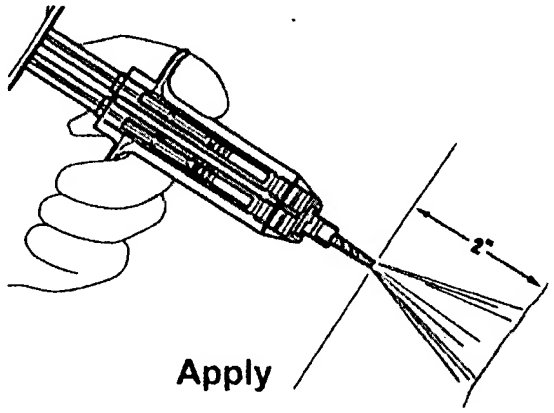


Interruption of the application for approximately 10 seconds may result in occlusion of the spray tip. If occlusion occurs, remove the spray tip, wipe the end of the applicator to remove any fluid, and attach a new spay tip (provided) onto the end of the applicator as described in step 8 of the ProGel™ Preparation section, above.

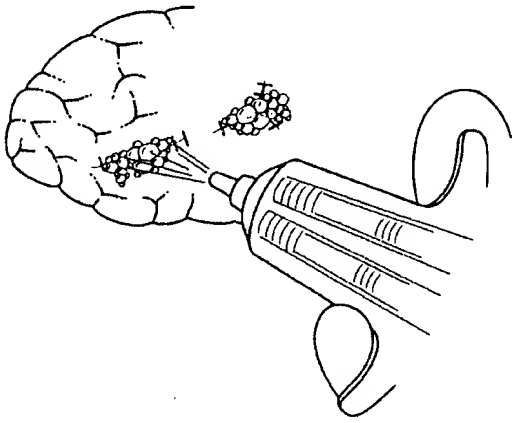
Keep the applicator tip approximately 5 cm (2 in.) away from the target area to avoid creating bubbles in the sealant material and apply with a smooth sweeping motion. The formation of bubbles may compromise the adherence and/or mechanical properties of the ProGel™.

Step 15. Select the target site to be sealed. (Note: Each 4 ml applicator will supply enough ProGel™ to cover an area 40 cm^2 (6 $in.^2$) and 1 mm thick.

Step 16. Hold the spray tip approximately 5 cm (2 in) from the tissue to be sealed, and apply firm, steady pressure to the pushrod to dispense the gel to the target location. Note: As described above, the gel can be applied in either a spray pattern or a stream depending upon the amount of pressure applied to the pushrod. Applying a light pressure will cause the gel to be dispensed in a stream. Applying slightly more pressure to the pushrod will cause the stream to convert to a spray.



Step 17. Maintain firm pressure on the pushrod and move the spray tip from side to side along the margin of the tissue surface to be sealed.



Step 18. Allow the ProGel™ to cure for 15-30 seconds, forming a flexible hydrogel. Two minutes after application, the ProGel™'s success in sealing the target site(s) can be tested using the saline submersion test or by irrigating the site to check for air bubbles.

Step 19. ProGel™ application over an AL site that leaks despite standard methods of closure, may be repeated up to a total of 3 applications per AL site if necessary to seal the AL. Thereafter, other methods for sealing an air leak should again be considered.

Step 20. If the applicator's contents are not entirely used in the first application, immediately remove the spray tip and wipe residual ProGel™ components from the applicator tip with clean dry gauze to prevent the remaining material from activating. Repeat application requires spray tip replacement of the previously used spray tip with an unused, sterile tip: an additional spray tip is provided in the kit.

Step 21. If more than one kit is needed, additional kits should be prepared and applied as needed.

11.0 HOW SUPPLIED

STERILE: ProGel™ Pleural Air Leak Sealant is supplied sterile, with total reconstituted component volume of 4 ml per ProGel™ unit. It is intended for single use only. Non-pyrogenic. Do not use if package is opened or damaged.

12.0 STORAGE

The ProGel™ should be refrigerated between 2°C to 8°C (36°F to 46°F). Do not freeze. Note: Store the ProGel™ within the recommended temperature range. Failure to do so may result in poor product performance.

ProGel™ is a Trademark of NeoMend, Inc.
NeoMend, Inc.
Irvine, CA 92618

EXHIBIT G

7.0 PROCEDURE:

7.1 Preparation of Buffer Solution
Prepare enough buffer solution for 12.5 times the volume of albumin to be processed.

Formulation:

COMPONENT AMOUNT per 1 liter of buffer.

Sterile, Pyrogen-Free Water 1 ± 0.05 L

Sodium Bicarbonate (NaHCO3) 5.73 ± 0.05 g (0.0682 gm/mole)

Sodium Chloride (NaCl)9.00 ± 0.05 g (0.1540 gm/mole).

Sodium Carbonate 0.72 ± 0.05 g (0.0068 gm/mole).

Hydroxide Acid (NC1) As required.

Sodium Hydroxide (NaOH) As Required.

7.1.1 Prepare the buffer solution in a Class 100 Clean Area.

7.1.2 Add sterile water for irrigation to mix tank.

7.1.3 Weigh out sodium bicarbonate, sodium chloride, and sodium carbonate and add to the mix tank while stirring.

7.1.4 Mix until solids are dissolved with a minimum mix time of 30 minutes.

7.1.5 Remove a sample of buffer from the bulk mixture and measure the pH.

7.1.6 If the pH is not between 8.85 and 8.95, add hydrochloric acid (to decrease the pH) or sodium hydroxide (to increase the pH) dropwise, with stirring.

7.1.7 Mix a minimum of 15 minutes then remove a sample of buffer from the bulk mixture to check the pH.

7.1.8 Repeat steps 7.1.6. and 7.1.7 until the pH of the buffer solution is between 8.85 end 8.95.

7.1.9 Check sodium level per Section 8.1.2.

EXHIBIT H

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Gretchen Keenan
Product Regulation Manager
3M Health Care
3M Center, Building 275-3E-08
St. Paul, Minnesota 55144-1000

JUN 29 1999

Re: G980283/A02
3M Polymeric Patch
Indications for Use: For Sealing Intraoperative Air Leaks Occurring during Pulmonary Resection
Dated: June 2, 1999
Received: June 3, 1999
HCFA Reimbursement Category: A1

Dear Ms. Keenan:

The Food and Drug Administration (FDA) has reviewed the amendment to your investigational device exemptions (IDE) application which addressed the deficiencies cited in our February 17, 1999 disapproval letter and proposed changes in the study protocol. Your application is conditionally approved and you may begin your investigation at the institutions listed in the enclosure in accordance with the investigational site waiver granted below. Your investigation is limited to 6 institutions and 10 subjects.

This approval is being granted on the condition that, within 45 days from the date of this letter, you submit information correcting the following deficiencies:

1. While the release specification for HSA polymers in the final product is less than 24 % HSA polymers, only 9.6% HSA polymers were detected after irradiation with the proposed e-bean sterilization dose of 12 kGy. Please revise the release specification for HSA polymers to be more consistent with the validation study results or provide information that explains why the HSA polymer release specification should be more then twice the concentration detected in the validation study.

2. Page 4 of the Appendix A states that, "The packaging configuration for sterilization of this product has not been decided." Please provide information that describes how changes in the packaging configuration could impact the dose-mapping study performed previously to

validate the sterilization conditions. For example, does the potential exist for underdosing or overdosing the amount of e-beam irradiation? If so, how was this assessed in your previous validation study?

The proposed revision to Section 7.1.3 (Adverse Events) states, "Events which are part of the study sites care maps will not be recorded as adverse events unless they are considered clinically different than expected." Because initial evaluations concerning the incidence, severity and causality of adverse events may change after a final review of the entire study results, it is important that all adverse events occurring during the study be recorded in the case report forms. Also Appendix E of your protocol lists adverse events that maybe related to the device. Please modify your protocol so that this document is not viewed as a complete list of adverse events related to the device. Please submit a revised protocol that addresses these concerns.

Regarding the new proposed primary effectiveness endpoint for your study, (i.e., the proportion of patients who remain free of postoperative air leaks for the duration of the study), please provide a revised protocol that addresses the following issues:

a. Please specify the endpoint with respect to the duration of follow-up. For example, the duration of freedom from air-leak could be identified as the duration of hospital stay or 30 days post-operatively, which ever is longer. We believe this will permit a more uniform monitoring of delayed device failures and also eliminate confusion between the total study duration and individual patient outcomes.

b. Please provide information that discusses how patients with incomplete data or lost to follow-up will be treated. FDA recommends that a statistical time-to-event model or survival analysis be prepared to compare cumulative proportions of air leak-free throughout all follow-up times for the 3M Patch and control groups by using information from all patients, including those have completed the study, those that are lost to follow-up and/or those censored with incomplete data for the revised binary (air leak versus air leak-free) clinical outcomes. The exclusion of patients lost to follow-up or censored patients from the analysis is subjected to bias since follow-up time varies from patient to patient in the 3M Patch and control groups.

5. The revised study size calculations presented in Section 11.1 suggest that a 110 treatment and 55 control patients must be enrolled to detect, in a statistically significant manner, a 25% difference in the proportion of patients with postoperative air leaks. Please submit a revised protocol that addresses the following concerns:

a. Your calculations are based on an anticipated dropout rate of 16%. We believe this value is unacceptably high when the majority of the patients will be hospitalized throughout the entire time period that they will be assessed for product effectiveness.

b. The study size calculations submitted in your application do not appear to have included considerations for an unequal group assignment (2:1 ratio) which are often larger than needed for an equal group assignment (1:1 ratio), based on the same pre-specified conditions for power, type I error, P_1 and P_2. For example our calculations suggest that 116 treatment and 58 control patients should be enrolled to observe a 25% decrease in the proportion of patients with post-operative air leaks (i.e., 65% versus 40%) assuming a 10% drop out rate, a power of 80% and type I error of 5% (two-sided). Please submit a revised protocol with a new study size calculation or provide information that clarifies the methods used to estimate the number of patients required to demonstrate a statistically significant clinical improvement in patient outcome.

This information should be identified as an IDE supplement referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

If you do not provide this information within 45 days from the date of this letter, we may take steps to propose withdrawal of approval of your IDE application.

FDA will waive those requirements regarding submission and prior FDA approval of a supplemental application and receipt of certification of institutional review board (IRB) approval for the addition of investigational sites (21 CFR 812.35(b)) provided:

1. The total number of investigational sites does not exceed 6.

2. You maintain current records on:

   a. the names and addresses of all investigational sites;

   b. the names and addresses of all investigators, identifying those that are currently participating;

   c. the names, addresses and chairpersons of all IRBs;

   d. the dates of IRB approvals; and

e. the dates of first shipments or first use of investigational devices for all participating institutions.

3. Within 5 days of reaching the investigational site limit, you submit to FDA a current list containing the information specified in 2(a-e) above.

4. The current investigator list to be submitted to FDA at 6-month intervals (21 CFR 812.150(b)(4)) will contain the information specified in 2(a-e) above.

5. You submit to FDA, within 2 days of receipt of a request by FDA, a current list containing the information specified in 2(a-e) above.

6. The reviewing IRB does not require any significant changes in the investigational plan or in the informed consent, that is, require any change which may increase the risks to subjects or affect the scientific soundness of the study. (Please note: If a significant change is requested, this change must be submitted to FDA for review and approval prior to initiating the study at that investigational site.) Minor changes requested by the IRB may be made without prior FDA approval.

If you agree to these conditions, you may begin an investigation at a new investigational site after the IRB has approved the investigation. No documentation should be submitted for any institution within the approved limit until the investigational site limit is reached or the 6-month current investigator list is due. FDA assumes that you have agreed to the conditions of this waiver unless you specifically notify us in writing of your disagreement. Please note, however, that you must submit a supplemental IDE application, and receive FDA approval, prior to expanding the investigation beyond the limit specified above. Additionally, if you do not agree to these conditions, you must comply with the full requirements for the submission to FDA of a supplemental IDE application for new investigational sites not already specifically approved for participation in your study (21 CFR 812.35(b)).

We would like to point out that FDA approval of your IDE application does not imply that this investigation will develop sufficient safety and effectiveness data to assure FDA approval of a premarket approval (PMA) application for this device. You may obtain the guideline for the preparation of a PMA application, entitled "Premarket Approval (PMA) Manual," from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597.

We have enclosed the guidance document entitled "Sponsor's Responsibilities for a Significant Risk Device Investigation" to help you understand the functions and duties of a sponsor. Also enclosed is the guidance document "Investigators' Responsibilities for a Significant Risk Device

Investigation" which you should provide to participating investigators.

If you have any questions, please contact Charles N. Durfor, Ph.D. at (301) 594-3090 ext. 134.

Sincerely yours,

Celia M. Witten, Ph.D., M.D.
Director
Division of General and
Restorative Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures
(1) Sponsor's Responsibilities for a Significant Risk Device Investigation
(2) Investigators' Responsibilities for a Significant Risk Device Investigation
(3) Procedures to Request Re-Evaluation of HCFA Reimbursement Categorization Determination
(4) Guidelines for the Monitoring of Clinical Investigations

EXHIBIT I

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

August 23, 2001

TIMOTHY J. KAPPERS
3M CO.
3M CENTER, BLDG. 275-5W-06
ST. PAUL, MN 55133

Dear MR. KAPPERS:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges receipt of your PMA ORIGINAL. This PMA ORIGINAL has been assigned the following unique document control number. Failure to reference this assigned number in future correspondence may result in processing delays.

PMA Number: P010047
Dated: 22-AUG-2001
Received: 23-AUG-2001
Device: 3M SURGICAL SEALANT

Any questions concerning this submission should be directed to the undersigned at (301)594-1184. All future correspondence regarding this PMA should be identified with the PMA number assigned above and should be submitted with the required number of copies to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

Sincerely yours,

Contractor @ J. Barge

Pauline Fogarty
Consumer Safety Officer
Division of General, Restorative,
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

EXHIBIT J

EXHIBIT J

Chronology of Regulatory Activities

Date	Type	Activity
October 30, 1998	IDE	Application for 3M Polymeric Patch Submitted to FDA by 3M Health Care
November 3, 1998	IDE G980283	FDA letter acknowledging IDE filed and assigning IDE No. G980283
December 2, 1998	IDE G980283	FDA Letter disapproving IDE Application for deficiencies
February 17, 1999	IDE G980283	FDA Letter disapproving amendment to IDE Application for deficiencies (A01)
June 2, 1999	IDE G980283	Second Amendment to IDE Application submitted to FDA (A02)
June 29, 1999	IDE G980283	FDA Letter issuing Conditional IDE Approval (A02)
August 19, 1999	IDE G980283	Addendum to IDE Supplement submitted to FDA (S001)
August 25, 1999	IDE G980283	FDA Letter issuing IDE Approval (S001)
November 2, 1999	IDE G980283	Notice of IDE Change submitted to FDA for minor modification in viscosity and percent albumin polymers (S002)
January 17, 2000	IDE G980283	Request for Expedited PMA Review submitted to FDA (S003)
January 25, 2000	IDE G980283	Report of Serious Adverse Event submitted to FDA (S004)
February 22, 2000	IDE G980283	Notice of IDE Change submitted to FDA for minor clinical protocol changes (S005)
March 1, 2000	IDE G980283	Current Investigator List submitted to FDA (S006)
March 28, 2000	IDE G980283	Report of Unanticipated Adverse Device Effect submitted to FDA (S007)
April 18, 2000	IDE G980283	Telephone Conference with FDA regarding March 28, 2000 Report of Unanticipated Adverse Device Effect
April 19, 2000	IDE G980283	Notice of IDE Change submitted to FDA for minor clinical protocol changes (S008)
April 26, 2000	IDE G980283	Response to FDA Questions relating to March 28, 2000 Report of Unanticipated Adverse Device Effect (S009)
May 31, 2000	IDE G980283	Response to Suggestions relating to Report of Unanticipated Adverse

		Device Effect (S010)
June 8, 2000	IDE G980283	Report of 3M Polymeric Patch Recall (5/12/00): Lot W504419 submitted to FDA (S011)
June 22, 2000	IDE G980283	Notice of Change in Investigational Plan submitted to FDA (S012)
July 18, 2000	IDE G980283	Addendum to Supplemental Application: Change in Investigational Protocol submitted to FDA (S013)
August 22, 2000	IDE G980283	Annual IDE Progress Report submitted to FDA (S014)
September 11, 2000	IDE G980283	Report of Serious Adverse Events submitted to FDA (S015)
October 23, 2000	IDE G980283	Notice of IDE Change for Change in Investigational Protocol submitted to FDA (S017)
March 15, 2001	IDE G980283	Current Investigator List and Notice of Cessation of Clinical Enrollment submitted to FDA (S018)
June 28, 2001	Pre-PMA	Pre-PMA filing meeting discussions
July 31, 2001	Pre-PMA	Pre-PMA filing meeting discussions
August 22, 2001	PMA	PMA for 3M Surgical Sealant-Pulmonary Use submitted to FDA by 3M Health Care
August 23, 2001	PMA P010047	FDA Letter acknowledging PMA filed and assigning PMA No. P010047
October 2, 2001	PMA P010047	FDA Letter acknowledging PMA Filing Date of August 23, 2001 and denial of expedited review
October 11, 2001	IDE G980283	IDE Final Report submitted to FDA (S019)
December 10, 2001	PMA P010047	FDA Letter Disapproving PMA for deficiencies
March 25, 2002	PMA P010047	PMA Amendment No. 1 submitted to FDA (A001)
March 26, 2002	PMA P010047	FDA Letter acknowledging PMA Amendment No. 1 filed (A001)
April 4, 2002	PMA P010047	PMA Amendment No. 2 submitted to FDA (A002)
April 8, 2002	PMA P010047	FDA Letter acknowledging PMA Amendment No. 2 filed (A002)
September 26, 2002	PMA P010047	PMA Amendment No. 3 submitted to FDA (A003)
September 27, 2002	PMA P010047	FDA Letter acknowledging PMA Amendment No. 3 filed (A003)

October 24, 2002	PMA P010047	PMA Amendment No. 4 submitted to FDA (A004)
October 28, 2002	PMA P010047	FDA Letter acknowledging PMA Amendment No. 4 filed (A004)
March 13, 2003	PMA P010047	PMA Amendment No. 5 submitted to FDA (A005)
March 14, 2003	PMA P010047	FDA Letter acknowledging PMA Amendment No. 5 filed (A005)
July 2, 2003	PMA P010047	FDA Letter Disapproving PMA with Amendments No. 1, 2, 3, 4, and 5
December 2, 2003	PMA P010047	PMA Amendment No. 6 submitted to FDA (A006)
December 4, 2003	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 6 filed (A006)
March 30, 2004	PMA P010047	PMA Amendment No. 7 submitted to FDA (A007)
March 31, 2004	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 7 filed (A007)
April 19, 2004	PMA P010047	Request for First Directed Hold and Notice of PMA Transfer of Ownership from 3M to Neomend, Inc. submitted to FDA (A008)
April 20, 2004	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 8 filed and Issuing First Directed Hold (A008)
June 25, 2007	PMA P010047	Request for Removal of First Directed Hold submitted to FDA (A009)
June 27, 2007	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 9 filed and Removal of First Directed Hold (A009)
October 4, 2007	PMA P010047	Request for Second Directed Hold submitted to FDA (A010)
October 10, 2007	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 10 filed and Issuing Second Directed Hold Request (A010)
November 1, 2007	PMA P010047	Request for Removal of Second Directed Hold submitted to FDA (A011)
November 2, 2007	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 11 filed and Removal of Second Directed Hold (A011)
January 21, 2008	PMA P010047	PMA Amendment No. 12 submitted to FDA (A012)
January 23, 2008	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 12 filed (A012)
March 7, 2008	PMA P010047	PMA Amendment No. 13 submitted to FDA (A013)
March 11, 2008	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 13 filed (A013)

July 14, 2008	PMA P010047	PMA Amendment No. 14 submitted to FDA (A014)
July 15, 2008	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 14 filed (A014)
July 29, 2008	PMA P010047	PMA Amendment No. 15 submitted to FDA (A015)
July 30, 2008	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 15 filed (A015)
August 18, 2008	PMA P010047	PMA Amendment No. 16 submitted to FDA (A016)
August 20, 2008	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 16 filed (A016)
October 9, 2008	PMA P010047	PMA Amendment No. 17 submitted to FDA (A017)
October 10, 2008	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 17 filed (A017)
	PMA P010047	PMA Amendment No. 18 submitted to FDA (A018)
November 13, 2008	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 18 filed (A018)
November 26, 2008	PMA P010047	PMA Amendment No. 19 submitted to FDA (A019)
November 26, 2008	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 19 filed (A019)
December 23, 2008	PMA P010047	FDA Letter regarding PMA 30-day Notice and confirming 135 day PMA supplement not required
February 5, 2009	PMA P010047	PMA Amendment No. 20 submitted to FDA (A020)
February 5, 2009	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 20 filed (A020)
March 10, 2009	PMA P010047	E-mail correspondence with FDA regarding teleconference
March 11, 2009	PMA P010047	Teleconference with FDA and notice of discussion points for teleconference with FDA
March 17, 2009	PMA P010047	E-mail correspondence with FDA providing answers to questions raised during March 11, 2009 teleconference relating to A019
March 18, 2009	PMA P010047	E-mail correspondence with FDA providing answers to questions raised during March 11, 2009 teleconference relating to A018
May 13, 2009	PMA P010047	FDA Notice of Inspection
July 27, 2009	PMA P010047	FDA Request for Additional Information relating to manufacturing process
July 29, 2009	PMA P010047	Response to FDA's Request for Additional Information relating to manufacturing process of July 27, 2009 submitted to FDA

July 29, 2009	PMA P010047	FDA Letter for Establishment Inspection Report
	PMA P010047	PMA Amendment No. 21 submitted to FDA (A021)
September 17, 2009	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 21 filed (A021)
September 30, 2009	PMA P010047	PMA Amendment No. 22 submitted to FDA (A022)
October 1, 2009	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 22 filed (A022)
October 29, 2009	PMA P010047	PMA Amendment No. 23 submitted to FDA (A023)
October 30, 2009	PMA P010047	FDA Letter Acknowledging PMA Amendment No. 23 filed (A023)
November 9, 2009	PMA P010047	FDA Notice of Inspection
January 14, 2010	PMA P010047	FDA PMA Approval Letter Issued

EXHIBIT K

neomend

June 25, 2007

Food and Drug Administration
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
9200 Corporate Blvd.
Rockville, MD 20850

Subject: PMA Amendment to P010047
Neomend™ ProGEL™ Surgical Sealant (Pulmonary Use)

To Whom It May Concern:

Neomend, Inc., hereby provides three copies to the FDA of an amendment to PMA P010047, originally submitted by the Medical Division of 3M Corporation for 3M™ Surgical Sealant (Pulmonary Use).

The purposes of this amendment are as follows:

1. Provide notification to the FDA and confirm the transfer of ownership of the subject PMA from 3M to Neomend, Inc., effective June 22, 2007. A letter from 3M to FDA providing notification of this transfer is included as an attachment to this cover letter.
2. To effect a change to the trade name of the device to ProGEL™ Surgical Sealant (Pulmonary Use).
3. To ask that the Directed Hold that was requested be put on PMA P010047 by 3M in correspondence to FDA dated April 19, 2004, be removed at the earliest time and the review cycle clock restarted.

Neomend, Inc., intends to make no changes to the PMA as it existed at the time it was placed on Directed Hold, and would like to proceed to panel review as soon as possible.

Thank you for your attention to this submission. Please contact me if you should have any questions or require additional information.

Sincerely,

John L. Gehrich
Vice President, Regulatory & Clinical
Neomend, Inc.
9272 Jeronimo, #119
Irvine, CA 92618
(949) 916-1630 X105
(949) 916-1635 Fax
jackg@neomendinc.com

ATTACHMENT

3M Letter to FDA Regarding Notification of Ownership Transfer

PMA P010047 – 3M Surgical Sealant (Pulmonary Use)

3M Health Care

3M Center, Bldg. 0275-05-W-06
St. Paul, MN 55144-1000
651 733 1110

3M

June 22, 2007

Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD 20850

Subject: Transfer Ownership of PMA P010047 - 3M™ Surgical Sealant (Pulmonary Use)

To Whom It May Concern:

The purpose of this letter is to notify the FDA of 3M's intent to transfer ownership of PMA P010047 - 3M™ Surgical Sealant (Pulmonary Use) and all rights to this PMA to Neomend, Inc. as of June 22, 2007. PMA P010047 is currently in the PMA review process and was placed on Directed Hold by 3M on April 19, 2004.

The Neomend, Inc. contacts for this PMA are:

Jack Gehrich
VP Regulatory and Clinical
Neomend, Inc.
9272 Jeronimo #119
Irvine, CA 92618

Jerry Mezger
President and CEO
Neomend, Inc.
9272 Jeronimo, #119
Irvine, CA 92618

3M has made a complete copy of the PMA, including all amendments and correspondence, available to Neomend, Inc. In addition, Neomend, Inc. has informed 3M of their intent to take the PMA off Directed Hold upon transfer of ownership.

Sincerely,

Suzanne M. Danielson

Suzanne M. Danielson
Director, Regulatory Affairs and Quality
Medical Division
3M Company
3M Center, Bldg. 275-5W-06
St. Paul, MN 55144-1000

cc: Dr. Charles Durfor, Mail Stop HFZ-410, 9200 Corporate Blvd., Rockville, MD 20850

EXHIBIT L

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

June 27, 2007

JOHN L. GEHRICH
NEOMEND, INC.
9272 JERONIMO RD
SUITE 119
IRVINE, CA 92618

Dear JOHN GEHRICH:
The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges receipt of your PMA AMENDMENT. This PMA AMENDMENT has been assigned the following unique document control number. Failure to reference this assigned number in future correspondence may result in processing delays.

PMA Number: P010047/A009
Dated: 25-JUN-2007
Received: 27-JUN-2007
Device: PROGEL SURGICAL SEALANT

Any questions concerning this submission should be directed to the undersigned at (240)276-3737. All future correspondence regarding this PMA should be identified with the PMA number assigned above and should be submitted with the required number of copies to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

In future premarket submissions, we encourage you to provide an electronic copy of your submission. By doing so, you will save FDA resources and may help reviewers navigate through longer documents more easily. Under CDRH's eCopies Program, you may replace one paper copy of any premarket submission (e.g., 510(k), IDE, PMA, HDE) with an electronic copy. For more information about the program, including the formatting requirements, please see www.fda.gov/cdrh/elecsub.html. To ensure the electronic copy is complete, it is essential that you: (1) state in your cover letter that you are providing an electronic copy as per FDAs instructions and that it is an exact duplicate of the paper copy and (2) follow the required structure of the files and/or folders described in the instructions with respect to the naming convention, descriptive names for files and folders, use of folders for volumes only, and placement at the root of the CD/DVD.

Sincerely yours,

Pauline Fogarty
Consumer Safety Officer
Division of General, Restorative,
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

EXHIBIT M

$40.00 581 Docket No. 50731USA6A A6

08/281473

PATENT ASSIGNMENT RECORDATION COVER SHEET

MAIL ROOM JUL 28 1994 TECH CENTER

To the Honorable Commissioner of Patents and Trademarks:

Please record the attached original document or copy thereof.

1. Name of conveying party(ies):
Thomas H. Barrows
Terry W. Lewis
Mynanh T. Truong

Additional names of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)

Minnesota Mining and Manufacturing Company
P.O. Box 33427
St. Paul, Minnesota 55133-3427

3. Nature of conveyance: ☒ Assignment 19

Execution Date(s): July 27, 1994

4. Application number or patent number:

☒ This document is being filed with a new patent application on July 27, 1994.

☐ This document is to be recorded against the following patent application or patent:

5. Name and address of party to whom correspondence concerning document should be mailed:

Paul W. Busse
Minnesota Mining and Manufacturing Company
Office of Intellectual Property Counsel
P.O. Box 33427
St. Paul, Minnesota 55133-3427

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41) $40.00

☐ Previously submitted
☒ Enclosed

8. ☒ Please charge any additional fees or credit any overpayment to Deposit Account No. 13-3723.

DO NOT USE THIS SPACE

93570824

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Paul W. Busse — Printed Name of Attorney
Paul W. Busse — Signature
July 27, 1994 — Date

10. Total number of pages including cover sheet, attachments, and document: 2

40 AM 08/04/94 08281473 1 581 40.00 CK 50731USA6A

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments, Washington, D.C. 20231

Docket No. 50731USASA

ASSIGNMENT

Whereas We, Thomas H. Barrows, Terry W. Lewis, and Myhanh T. Truong, with residences and citizenships as indicated below, have made an invention in

ADHESIVE SEALANT COMPOSITION

and have today executed an application for Letters Patent of the United States of America based thereon;

Now, therefore, for good and valuable consideration, receipt of which is acknowledged, we have individually and jointly agreed to assign and transfer and do hereby assign and transfer unto the MINNESOTA MINING AND MANUFACTURING COMPANY (sometimes designated as the Minnesota Mining & Manufacturing Company), a corporation of Delaware, having its principal office at Saint Paul, Minnesota, its successors and assigns, the entire right, title, and interest in and to the said invention and application, and in and to any division or continuation (in whole or in part) of said application, and in and to any and all improvements in the said invention made by us or any of us or made jointly with others (provided any such improvement is made during, or within one year after the termination of, the employment by the said Company of whichever of us, solely or jointly with one or more others, has made the same), and in and to any and all Letters Patent, reexaminations, reissues, or extensions thereof, of the United States of America and countries foreign thereto (including the right to apply for Letters Patent, Utility Models, or Inventors' Certificates in foreign countries in its own name and to claim any priority rights for such foreign applications to which such applications are entitled under international conventions, treaties, or otherwise), which have been or may be granted thereon or on any divisional, continuation (in whole or in part), renewal, reexamination, reissue, or other or further application based in whole or in part upon the said invention or improvements thereon, to be held and enjoyed as fully and exclusively as they would have been by us or any of us had this assignment and transfer not been made,

We do further agree for ourselves and for our heirs, executors, and administrators, to execute and deliver without further consideration any further applications, assignments, and documents, and to perform such other acts as we lawfully may, that may be deemed necessary by the said Company, its successors, assigns, and nominees, fully to secure its right, title, and interest as aforesaid and to obtain or maintain Letters Patent, Utility Models, or Inventors' Certificates in any and all countries;

And we do hereby authorize and request the Commissioner of Patents to issue any and all Letters Patent which may be granted upon any of the said applications, to the said Minnesota Mining and Manufacturing Company, as the assignee of the entire right, title, and interest therein.

In witness whereof, we have hereunto signed our names on the days and years set forth below.

RECORDED 123 FRAME 961

Inventor 1: Thomas H. Barrows
Residence: City of Cottage Grove, County of Washington, State of Minnesota
Citizenship: United States of America

Inventor 2: Terry W. Lewis
Residence: City of Woodbury, County of Washington, State of Minnesota
Citizenship: United States of America

Inventor 3: Myhanh T. Truong
Residence: City of Blaine, County of Anoka, State of Minnesota
Citizenship: United States of America

JUL 27 94

PATENT AND TRADEMARK OFFICE

STATE OF MINNESOTA }
} ss.
COUNTY OF RAMSEY }

On this 27th day of July, 1994, before me personally appeared the above-named Thomas H. Barrows, Terry W. Lewis, and Myhanh T. Truong, personally known by me, and known by me to be the persons described in and who executed the foregoing instrument, and who acknowledged that they executed the same as their free act and deed, on the day and year aforesaid.

(Seal)

SUSAN P. GUMATZ
NOTARY PUBLIC—MINNESOTA
WASHINGTON COUNTY
My Comm. Expires Mar. 18, 1997

Susan P. Gumatz
Notary Public

EXHIBIT N

Substitute Form PTO-1595

11-10-1998

100874853

Attorney Docket No.: 09125/001001

SHEET

Assistant Commissioner for Paten

ocument.

MED 11-4-98

1. Name of conveying party(ies):
Matthew T. Scholz

Additional name(s) attached? ☐ Yes ■ No

2. Name and address of receiving party(ies):
Minnesota Mining and Manufacturing Company
po Box 33427
St. Paul, Minnesota 55133-3427

Additional names/addresses attached? ☐ Yes ■ No

3. Nature of conveyance:
- ■ Assignment
- ☐ Merger
- ☐ Security Agreement
- ☐ Change of Name
- ☐ Other:

Execution Date: **October 2, 1998**

4. Application number(s) or patent number(s):
If this document is being filed with a new application, the execution date of the application is:

A. Patent Application No.(s):
07/281,473

B. Patent No.(s):
5,583,114

Additional numbers attached? ☐ Yes ■ No

5. Name/address of party to whom correspondence concerning document should be mailed:

John J. Gagel
Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804

6. Total number of applications/patents involved: **1**

7. Total fee (37 CFR 3.41): **$40**
- ■ Enclosed
- ☐ Authorized to charge deposit account

8. Deposit account number: **06-1050**
If the fee above is being charged to deposit account, a duplicate copy of this cover sheet is attached. Please apply any additional charges, or any credits, to our Deposit Account No. 06-1050.

DO NOT USE THIS SPACE

9. Statement and signature: *To the best of my knowledge and belief, the foregoing information is true and correct and the attached is the original document.*

John J. Gagel — 11/4/98
Name of Person Signing — Signature — Date

Total number of pages including cover sheet, attachments, and document: 2

EL187579734US

November 4, 1998

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231

Maureen T. Whale

Maureen T. Whale

Date of Deposit

I hereby certify under 37 CFR 1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

ASSIGNMENT

For valuable consideration, I, Matthew T. Scholz, of Woodbury, Minnesota hereby assign to Minnesota Mining and Manufacturing Company, a Minnesota corporation having a place of business at PO Box 33427, St. Paul, Minnesota, and its successors and assigns (collectively hereinafter called "the Assignee"), the entire right, title and interest throughout the world in the inventions and improvements which are subject of an application for United States Patent signed by me, entitled ADHESIVE SEALANT COMPOSITION, filed July 27, 1994, and assigned U.S. Serial Number 07/281,473, and granted U.S. Patent No. 5,583,114, and I authorize and request the attorneys appointed in said application to hereafter complete this assignment by inserting above the filing date and serial number of said application when known; this assignment including said application, any and all United States and foreign patents, utility models, and design registrations granted for any of said inventions or improvements, and the right to claim priority based on the filing date of said application under the International Convention for the Protection of Industrial Property, the Patent Cooperation Treaty, the European Patent Convention, and all other treaties of like purposes; and I authorize the Assignee to apply in all countries in my name or in its own name for patents, utility models, design registrations and like rights of exclusion, and for inventors' certificates for said inventions and improvements; and I agree for me and my respective heirs, legal representatives and assigns, without further compensation, to perform such lawful acts and to sign such further applications, assignments, Preliminary Statements and other lawful documents as the Assignee may reasonably request to effectuate fully this assignment.

IN WITNESS WHEREOF, I hereto set my hand and seal at St. Paul, Minnesota, U.S.A.,

this 2nd day of October, 1998

Matthew T. Scholz L.S.

Matthew T. Scholz

STATE OF MINNESOTA :

:ss.

COUNTY OF RAMSEY :

Before me this 2nd day of October, 19 98, personally appeared

Matthew T. Scholz known to me to be the person whose name is subscribed to the foregoing Assignment, and acknowledged that he/she executed the same as his/her free act and deed for the purposes therein contained.

Kathleen M. Sandvig

Notary Public

[Notary's Seal Here]

KATHLEEN M. SANDVIG
NOTARY PUBLIC - MINNESOTA
WASHINGTON COUNTY
My Comm. Expires Jan. 31, 2000

"Express Mail" mailing label number EL182571374US
Date of Deposit: November 4, 1998
I hereby certify that this paper or fee is being deposited with United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated and is addressed to the Commissioner of Patents and Trademarks Washington, D.C. 20231

Maureen T. Whalen

Maureen T. Whalen

Date of Deposit

I hereby certify under 37 CFR 1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

EXHIBIT O

Case No 50731US008

RECORDATION FORM COVER SHEET
PATENTS ONLY

To. The Director of the U.S. Patent and Trademark Office:

Please record the attached document(s) or the new address(es) below.

1. Name of conveying party(ies) Execution Date(s):

3M Company (formerly Minnesota Mining and Manufacturing Company), a Corporation of the State of Delaware — September 9, 2004

Additional name(s) of conveying party(ies) attached?
☐ Yes ☒ No

2. Name and address of receiving party(ies):

3M Innovative Properties Company
P.O. Box 33427
St. Paul, Minnesota 55133-3427

Additional name(s) of receiving party(ies) attached?
☐ Yes ☒ No

3. Nature of conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other:

4. Application or patent number(s) ☐ This document is being filed together with a new application.

A. Patent Application No(s).	B. Patent No(s).
10/293989	RE 38158

Additional Numbers Attached? ☐ Yes ☒ No

5. Name and address to whom correspondence concerning document should be mailed:

Name: Daniel R. Pastirik
Office of Intellectual Property Counsel
3M Innovative Properties Company
Phone Number: (651) 737-2685
Fax Number: 651-736-3833

32692
Customer Number

6. Total number of applications and patents involved: 2

7. Total fee (37 CFR §§ 1.21(h) & 3.41): **$80.00**
☐ Enclosed
☒ Authorized to be charged to deposit account

8. Payment Information:
Deposit Account Number: 13-3723
Authorized User Name: Daniel R. Pastirik

9. Signature:
Printed Name of Attorney/Agent:
Daniel R. Pastirik
Registration No.: 33,025

Daniel R. Pastirik — Signature
Sept. 10, 2004 — Date

Pages: Total number of pages including COVER SHEET, attachments, and documents: 2

Documents to be recorded (including cover sheet) should be faxed to (703) 306-5995, or mailed to:
Mail Stop Assignment Recordation Services, Director of the USPTO, P.O. Box 1450, Alexandria, VA 22313-1450

CH $80.00 13723 10293989

Case No : 50731US008

ASSIGNMENT

ASSIGNOR: 3M COMPANY (formerly MINNESOTA MINING AND MANUFACTURING COMPANY)
of: PO Box 33427
St. Paul, Minnesota 55133-3427
United States of America

a corporation organized and existing under the laws of the State of Delaware, United States of America does hereby claim and declare that it is the owner of all right, title and interest in and to the following Patent Application(s) or letters Patents(s) and other rights and powers obtainable or exercisable in respect thereof as numbered in United States Patent(s) and /or Patent Application(s):

Patent Application No.	Patent Number	Filing Date	Issue Date
10/293989		November 14, 2002	
	RE 38158		June 24, 2003

3M Company (formerly Minnesota Mining and Manufacturing Company) does hereby, for good and valuable consideration, effective as of April 1, 1999, received, sell, assign and transfer unto:

ASSIGNEE: 3M INNOVATIVE PROPERTIES COMPANY
of: PO Box 33427
St. Paul, Minnesota 55133-3427
United States of America

a corporation organized and existing under the laws of the State of Delaware, United States of America, its entire right, title and interest in and to the said Patent Application(s) or Letters Patent(s) including any division, continuation (in whole or in part) reissue or reexamination thereof, and in and to any countries foreign thereto, and consent to the recordal of this Assignment.

ASSIGNOR
Subscribed and Sworn:

At St. Paul, Minnesota 55133-3427
this 9th day of September, 2004

3M COMPANY (formerly MINNESOTA MINING AND MANUFACTURING COMPANY)

By: Carolyn A. Bates
Name: Carolyn A. Bates
Its: Assistant Chief Intellectual Property Counsel

Subscribed and sworn to before me this
9th day of September, 2004

Notary Public

CHERYL A. SAVER
NOTARY PUBLIC MINNESOTA
My Comm. Expires Jan. 31 2005

ASSIGNEE
Accepted:

At St. Paul, Minnesota 55133-3427
this 10th day of September, 2004

3M INNOVATIVE PROPERTIES COMPANY

By:
Name: Gary L. Griswold
Its: President and Chief Intellectual Property Counsel

Subscribed and sworn to before me this
10th day of September, 2004

Notary Public

JEAN S. KISTLER
NOTARY PUBLIC MINNESOTA
My Comm. Expires Jan. 31 2005

EXHIBIT P

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
3M Innovative Properties Company	06/21/2007

RECEIVING PARTY DATA

Name:	NeoMend, Inc.
Street Address:	60 Technology Drive
City:	Irvine
State/Country:	CALIFORNIA
Postal Code:	92618

PROPERTY NUMBERS Total: 12

Property Type	Number
Patent Number:	5502092
Patent Number:	5856367
Patent Number:	5583114
Patent Number:	RE38158
Patent Number:	RE38827
Patent Number:	6458095
Patent Number:	6569113
Patent Number:	6648852
Patent Number:	6576263
Patent Number:	6802822
Patent Number:	7037289
Application Number:	08956308

OP $480.00 5502092

CORRESPONDENCE DATA

Fax Number: (412)281-0717

Correspondence will be sent via US Mail when the fax attempt is unsuccessful.

Phone:	4124545000
Email:	docketingpgh@pepperlaw.com
Correspondent Name:	Pepper Hamilton LLP
Address Line 1:	One Mellon Center, 50th Floor
Address Line 2:	500 Grant Street
Address Line 4:	Pittsburgh, PENNSYLVANIA 15219-2502

ATTORNEY DOCKET NUMBER:	136071.2
NAME OF SUBMITTER:	Raymond A. Miller

Total Attachments: 4
source=NeoMendAssignment#page1.tif
source=NeoMendAssignment#page2.tif
source=NeoMendAssignment#page3.tif
source=NeoMendAssignment#page4.tif

PATENTS ASSIGNMENT

WHEREAS, 3M Innovative Properties Company, corporation of the State of Delaware, with offices at 3M Center, 2501 Hudson Road, Saint Paul, Minnesota 55144 ("Assignor") entered into an Asset Purchase and License Agreement dated , 2007 with Neomend, Inc., a corporation of Delaware, with offices at 272 Jeronimo, Suite 119, Irvine, California 92618 ("Assignee"); and

WHEREAS, Assignor is the owner or a joint owner with a third party of the Assigned Patents set forth on the attached Schedule A;

WHEREAS Assignee is desirous of obtaining Assignor's entire right, title and interest in, to and under the Assigned Patents;

NOW THEREFORE, in consideration of the sum of One Dollar ($1.00) paid to us in hand, and other good and valuable consideration, the receipt of which is hereby acknowledged, Assignor does hereby sell, assign, transfer and quitclaim unto Assignee, its successors and assigns, the entire right, title and interest of Assignor in and to the patents and applications listed on the attached pages, any and all patents issuing from any such patent applications, and any and all continuations, continuations-in-part, divisions, reissues, supplemental protection certificates, or extensions of any such patents and applications (collectively, the "Assigned Patents"), and the inventions and discoveries set forth therein, and Assignor's right to file applications on such inventions and discoveries, the same to held and enjoyed by the Assignee, for its own use and behalf and the use and behalf of its successors and assigns, to the full end of the term or terms for which Letters Patent or Patents may be granted as fully and entirely as the same would have been held and enjoyed by the Assignor had this sale and assignment not been made, and Assignor hereby authorizes and requests the Commissioner or Director of Patents and Trademarks of the United States and any official of any foreign country whose duty it is to issue patents, to issue or transfer all Letters Patent for the Patents to Assignee, its successors and assigns, in accordance with the terms of the assignment, or otherwise as Assignees may direct.

This Assignment is binding on Assignor, its successors and assigns, and will inure to the benefit of the Assignee, its successors and assigns. Nothing in this instrument, express or implied, is intended or shall be construed to confer upon, or give to, any person, corporation or entity other than Assignee, its successors and assigns, any remedy or claim under or by reason of this instrument, or any terms, covenants or conditions hereof, and all the terms, covenants and conditions in this instrument shall be for the sole and exclusive benefit of Assignee and its successors and assigns. Further, notwithstanding anything in this Assignment to the contrary, in the event of any conflict the Asset Purchase and License Agreement shall control.

IN WITNESS WHEREOF, Assignor has caused this Assignment to be executed this 21st day of June, 2007.

3M INNOVATIVE PROPERTIES COMPANY, a Delaware corporation

By: _____
Robert V. Sprague
Its: Secretary

Accepted this _____ day of June, 2007.

NEOMEND, INC. a Delaware corporation

By: _____

Its: President & CEO

August 18, 2009

SCHEDULE A

ASSIGNED PATENT RIGHTS

Biocompatible Porous Matrix Of Bioabsorbable Material					
Case Number	Case Type	Status	Patent Number	Application Number	Expiration
49904US007	ORD	Issued	5502092	08/198906	2/18/2014
49904US006	DIV	Issued	5856367	08/674679	1/5/2016
49904WO005	ORD	National		US95/01772	
49904CA002	PCT	Abandoned		2182279	2/13/2015
49904EP003	PCT	Issued	0744969	95910980.2	2/13/2015
49904DE003	EPC	Issued	69527042.7	95910980.2	2/13/2015
49904FR003	EPC	Issued	0744969	95910980.2	2/13/2015
49904GB003	EPC	Issued	0744969	95910980.2	2/13/2015
49904IT003	EPC	Issued	0744969	95910980.2	2/13/2015
49904JP004	PCT	Issued	3488687	521861/95	2/13/2015
Adhesive Sealant Composition					
Case Number	Case Type	Status	Patent Number	Application Number	Expiration
50731US007	ORD	Issued	5583114	08/281473	7/27/2014
50731US006	REI	Issued	RE 38158	09/185732	7/27/2014
50731US008	REI	Issued	RE 38527	10/293989	7/27/2014
50731WO005	ORD	National		US95/07947	
50731CA002	PCT	Issued	2194681	2194681	6/23/2015
50731EP003	PCT	Issued	0772464	95924047.4	6/23/2015
50731DE003	EPC	Issued	69529076.4	95924047.4	6/23/2015
50731ES003	EPC	Issued	0772464	95924047.4	6/23/2015
50731FR003	EPC	Issued	0772464	95924047.4	6/23/2015
50731GB003	EPC	Issued	0772464	95924047.4	6/23/2015
50731JP004	PCT	Issued	3592778	505739/96	6/23/2015
Dispenser For An Adhesive Sealant					
Case Number	Case Type	Status	Patent Number	Application Number	Expiration
53724US002	ORD	Abandoned		08/966308	
53724US008	CIP	Issued	6458095	09/524141	10/22/2017
53724US013	DIV	Issued	6569113	10/218406	10/22/2017
53724US014	DIV	Issued	6648852	10/400253	10/22/2017
53724WO007	ORD	National		US01/06916	
53724EP008	PCT	Published		01918333.4	3/2/2021
53724DE008	EPC	Unfiled			
53724ES008	EPC	Unfiled			
53724FR008	EPC	Unfiled			
53724GB008	EPC	Unfiled			
53724IT008	EPC	Unfiled			

Delivery Systems Using Preformed Biodegradable Polymer Compositions					
Case Number	Case Type	Status	Patent Number	Application Number	Expiration
54332US002	ORP	Issued	6576263	60/183560/784934	
54332WO004	ORD	National		US01/05020	2/16/2021
54332AU010	PCT	Issued	2001238384	2001238384	3/02/2021
54332BR012	PCT	Pending		PI0108471-2	
54332CA008	PCT	Pending		2398668	
54332CN013	PCT	Issued	01805066.2	01805066.2	2/16/2021
54332EP005	PCT	Published		01910817.4	2/16/2021
54332DE005	EPC	Unfiled			
54332FR005	EPC	Unfiled			
54332GB005	EPC	Unfiled			
54332IT005	EPC	Unfiled			
54332SE005	EPC	Unfiled			
54332JP007	PCT	Pending		2001-559433	2/16/2021
54332KR011	PCT	Pending		2002-7010681	2/16/2021
54332MX009	PCT	Pending		2002007938	2/16/2021

Dispenser For An Adhesive Tissue Sealant Having A Flexible Link					
Case Number	Case Type	Status	Patent Number	Application Number	Expiration
55503US002	ORD	Issued	6802822	09/540592	5/21/2021
55503WO003	ORD	National		US00/28190	
55503EP004	PCT	Published		00975239.5	10/12/2020
55503DE004	EPC	Unfiled			
55503FR004	EPC	Unfiled			
55503GB004	EPC	Unfiled			
55503IT004	EPC	Unfiled			
55503JP005	PCT	Pending		2001-572001	10/12/2020

Apparatus And Methods For Dispensing An Adhesive Tissue Sealant					
Case Number	Case Type	Status	Patent Number	Application Number	Expiration
56896US002	ORD	Issued	7037289	09/953037	09/12/2021
56896WO003	ORD	National		US02/24792	
56896BR004	PCT	Pending		PI0212005-4	
56896CA005	PCT	Pending		2460193	8/6/2022
56896EP006	PCT	Issued	1425107	02761238.1	8/6/2022
56896DE006	EPC	Issued	60211184.6	02761238.1	8/6/2022
56896FR006	EPC	Issued	1425107	02761238.1	8/6/2022
56896GB006	EPC	Issued	1425107	02761238.1	8/6/2022
56896JP007	PCT	Pending		2003-526576	8/6/2022

EXHIBIT Q

3M Health Care

3M Center
St. Paul, MN 55144-1000
651 733 1110

3M

October 11, 2001

Food and Drug Administration
Center for Devices and Radiological Health
IDE Document Mail Center (HFZ-401)
9200 Corporate Boulevard
Rockville, Maryland 20850

Re: IDE Final Report
IDE Number G980283/S19
3M™ Surgical Sealant – Pulmonary Use

Indications For Use: The Sealant is intended as an adjunct to standard tissue closure techniques for sealing or reducing air leaks (ALs) incurred during pulmonary surgery.

Attn.: Dr. Charles N. Durfor

Dear Dr. Durfor:

3M submits three copies of supplement number 19 to the above referenced IDE. Pursuant to 21 CFR 812.150(b)(7) and the conditions of IDE approval, 3M is submitting an IDE Final Report and related information.

The IDE Final Report follows FDA's format, as suggested in HHS Publication FDA 96-4159, June 1996 (Investigational Device Exemption Manual). This report summarizes 3M's Sugical Sealant clinical experice under IDE G980283, please refer to PMA P010047 for further detail.

Thank you for your attention to this matter. Please contact me at (651) 736-8371 if you have any additional questions.

Sincerely yours,

Timothy J. Kappers, RAC
Sr. Regulatory Affairs Associate
Medical-Surgical Division
3M Health Care
Phone Number: (651) 736-8371
Fax Number: (651) 737-5320
e-mail Address: tjkappers@mmm.com

EXHIBIT R

3M Health Care Markets

3M Center
St. Paul, MN 55144-1000
651 733 1110

3M

April 19, 2004

Food and Drug Administration
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
9200 Corporate Blvd.
Rockville, MD 20850

RE: P010047 - 3M™ Surgical Sealant (Pulmonary Use)

To Whom It May Concern:

The purpose of this letter is to request that the 3M Surgical Sealant (Pulmonary Use) PMA P010047 be put on Directed Hold by the FDA. 3M is requesting this Directed Hold based on business issues and the public nature of the pending Panel Review. By doing this we understand that the Panel Review scheduled for May 12, 2004 will be canceled. We also understand that this Directed Hold will result in the PMA review cycle clock being stopped.

3M agrees to provide the FDA with a minimum three-month notification prior to requesting this Directed Hold be removed. 3M will provide this notification in writing and will request confirmation of receipt from the FDA. 3M understand that the PMA review cycle clock will be restarted following the three-month notification period.

We appreciate the guidance provided by the FDA regarding this situation. If you have any questions regarding this request please contact me directly at either (651) 733-4365 (office) or (651) 283-7536 (cell). Thank you.

Sincerely,

Suzanne M. Danielson

Suzanne M. Danielson
Director of Regulatory Affairs and Quality
Medical Division
3M Center 275-5W-06
St. Paul, MN 55144-1000

EXHIBIT S

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

April 20, 2004

TIMOTHY J. KAPPERS
3M COMPANY
3M CENTER, BLDG. 275-5W-06
ST. PAUL, MN 55133

Dear MR. KAPPERS:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges receipt of your PMA AMENDMENT. This PMA AMENDMENT has been assigned the following unique document control number. Failure to reference this assigned number in future correspondence may result in processing delays.

PMA Number: P010047/A008
Dated: 19-APR-2004
Received: 20-APR-2004
Device: 3M SURGICAL SEALANT

Any questions concerning this submission should be directed to the undersigned at 594-1184. All future correspondence regarding this PMA should be identified with the PMA number assigned above and should be submitted with the required number of copies to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

Sincerely yours,

Pauline Fogarty
Consumer Safety Officer
Division of General, Restorative,
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

EXHIBIT T

neomend

October 4, 2007

Food and Drug Administration
PMA Document Mail Center (HFZ 401)
Center for Devices and Radiological Health
9200 Corporate Blvd.
Rockville, MD 20850

By Fax: (240) 276-3733

Re: PMA P010047 - ProGEL™ Surgical Sealant

Attn: Charles N. Durfor, DGRND/PRSB

To Whom It May Concern:

This letter is to request that the ProGEL Surgical Sealant PMA P010047 be put on Directed Hold by the FDA. The purpose of this request is to allow Neomend sufficient time to more thoroughly prepare for a panel meeting to consider the subject PMA. Neomend plans to submit an amendment to the PMA no later than November 5, 2007, which will contain new information for FDA's consideration that is not presently included in the existing PMA application. At the time of submission of the PMA amendment, Neomend will request that P010047 be removed from Directed Hold. Neomend then expects to be in a position to submit a draft Panel Package for this PMA to the FDA no later than December 3, 2007 and to participate in a panel meeting by February 1, 2008.

Thank you for your consideration in this matter.

Sincerely,

John L. Gehrich
Neomend, Inc.

cc: GJP

9272 Jeronimo, Suite 119 Irvine, California 92618
Tel. 949.916.1630 Fax. 949.916.1635 www.neomendinc.com

EXHIBIT U

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

October 10, 2007

JOHN L. GEHRICH
NEOMEND, INC.
9272 JERONIMO RD
SUITE 119
IRVINE, CA 92618

Dear JOHN GEHRICH:
The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges receipt of your PMA AMENDMENT. This PMA AMENDMENT has been assigned the following unique document control number. Failure to reference this assigned number in future correspondence may result in processing delays.

PMA Number: P010047/A010
Dated: 04-OCT-2007
Received: 10-OCT-2007
Device: PROGEL SURGICAL SEALANT

Any questions concerning this submission should be directed to the undersigned at (240)276-3737. All future correspondence regarding this PMA should be identified with the PMA number assigned above and should be submitted with the required number of copies to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

In future premarket submissions, we encourage you to provide an electronic copy of your submission. By doing so, you will save FDA resources and may help reviewers navigate through longer documents more easily. Under CDRH's eCopies Program, you may replace one paper copy of any premarket submission (e.g., 510(k), IDE, PMA, HDE) with an electronic copy. For more information about the program, including the formatting requirements, please see www.fda.gov/cdrh/elecsub.html. To ensure the electronic copy is complete, it is essential that you: (1) state in your cover letter that you are providing an electronic copy as per FDAs instructions and that it is an exact duplicate of the paper copy and (2) follow the required structure of the files and/or folders described in the instructions with respect to the naming convention, descriptive names for files and folders, use of folders for volumes only, and placement at the root of the CD/DVD.

Sincerely yours,

for Pauline Fogarty
Consumer Safety Officer
Division of General, Restorative,
and Neurological Devices
Office of Device Evaluation
Center for Devices and

EXHIBIT V

NeoMend Confidential

neomend

November 1, 2007

Food and Drug Administration
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
9200 Corporate Blvd.
Rockville, MD 20850

Subject: PMA P010047/A11
ProGEL™ Surgical Sealant

Dear Dr. Durfor:

NeoMend, Inc., hereby provides three copies to the FDA of Amendment number 11 to PMA P010047. The purpose of this amendment is to request that PMA P010047 be removed from the Directed Hold requested by NeoMend in Amendment A10; to redefine the maximum e-Beam sterilization dose levels to be used for the proposed ProGEL commercial product; and to further address concerns presented in FDA's correspondence of July 2, 2003, and raised again in our meeting of August 30, 2007, regarding extent of lung inflation and existence of pneumothorax (PTX) in treatment patients versus controls at the one month follow-up (1 MFU) chest x-ray (CXR) point.

Redefinition of Maximum e-Beam Sterilization Dose Levels:

NeoMend intends to reinstate the maximum e-Beam sterilization dose levels used for the Surgical Sealant used in the clinical study conducted by the PMA applicant (NeoMend or 3M, hereinafter referred to as "Applicant") under IDE number G980283, and withdraw the proposal in the original PMA P010047 submission for increased dose levels for the commercial product that was the subject of this PMA.

The following brief chronology is provided as background regarding events and interactions between Applicant and the FDA concerning maximum e-beam dose levels for the two chemistries which comprise the proposed ProGEL commercial product.

- 8/25/99: Applicant receives approval of IDE G980283 under which it is defined that the albumin component of the Investigational Device to be used in this pivotal clinical study will be exposed to a target e-beam irradiation dose of 12 kGy which was selected to insure a minimum dose of 11 kGY and a maximum dose of 14 kGy.
- 4/01: Applicant completes the pivotal study for the Applicant ReSure Surgical Sealant after having enrolled 161 patients; 103 Treatment and 58 Control patients.

9272 Jeronimo, Suite 119 Irvine, California 92618
Tel. 949.916.1630 Fax. 949.916.1635 www.neomendinc.com

EXHIBIT W

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

November 02, 2007

JOHN L. GEHRICH
NEOMEND, INC.
9272 JERONIMO RD
SUITE 119
IRVINE, CA 92618

Dear JOHN GEHRICH:
The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) acknowledges receipt of your PMA AMENDMENT. This PMA AMENDMENT has been assigned the following unique document control number. Failure to reference this assigned number in future correspondence may result in processing delays.

PMA Number: P010047/A011
Dated: 01-NOV-2007
Received: 02-NOV-2007
Device: PROGEL SURGICAL SEALANT

Any questions concerning this submission should be directed to the undersigned at (240)276-3737. All future correspondence regarding this PMA should be identified with the PMA number assigned above and should be submitted with the required number of copies to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

In future premarket submissions, we encourage you to provide an electronic copy of your submission. By doing so, you will save FDA resources and may help reviewers navigate through longer documents more easily. Under CDRH's eCopies Program, you may replace one paper copy of any premarket submission (e.g., 510(k), IDE, PMA, HDE) with an electronic copy. For more information about the program, including the formatting requirements, please see www.fda.gov/cdrh/elecsub.html. To ensure the electronic copy is complete, it is essential that you: (1) state in your cover letter that you are providing an electronic copy as per FDAs instructions and that it is an exact duplicate of the paper copy and (2) follow the required structure of the files and/or folders described in the instructions with respect to the naming convention, descriptive names for files and folders, use of folders for volumes only, and placement at the root of the CD/DVD.

Sincerely yours,

for Pauline Fogarty
Consumer Safety Officer
Division of General, Restorative,
and Neurological Devices
Office of Device Evaluation
Center for Devices and

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.10

APPLICANTS:	BARROWS, et al
TITLE:	ADHESIVE SEALANT COMPOSITION
PATENT NO.:	RE38,158
ATTORNEY REF:	136071.00016
DATE OF DEPOSIT:	April 8, 2010
EXPRESS MAIL NO.	EV472066223US

I HEREBY CERTIFY THAT THIS SUBMISSION OF:

☒ SUPPLEMENT TO APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. § 156 WITH LETTER DATED APRIL 5, 2010 FROM 3M TO NEOMEND (3 PAGES) – (ORIGINAL AND 2 COPIES); AND

☒ POSTCARD

IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE VIA UNITED STATES POST OFFICE EXPRESS MAIL UNDER 37 C.F.R. § 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO MAIL STOP HATCH-WAXMAN PTE, COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450.

Paula J. Watson
(Typed or printed name of person mailing paper or fee)

Paula J Watson
(Signature of person mailing paper or fee)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: RE 38,158	)
Inventors: Barrows, et al.	) EXPRESS MAIL NO.:
Assignee: Neomend, Inc.	) EV472066223US
	)
Issued: June 24, 2003	)
Title: ADHESIVE SEALANT COMPOSITION	)

Atty. Docket No. 136071.00016

Customer No. 21269

Mail Stop: Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENT TO APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. § 156

Dear Commissioner:

On March 2, 2010, Applicant, Neomend, Inc. ("Neomend"), owner of U.S. Reissued Patent No. RE38,158 (the "'158 Patent"), submitted an Application for Patent Term Extension Under 35 U.S.C. § 156 through its duly authorized agent named below.

At this time, Neomend wishes to supplement its application with the attached Letter from 3M Company ("3M"), d/b/a 3M Health Care and 3M Innovative Properties Companies, to Neomend dated April 5, 2010. In its Letter, 3M authorizes Neomend to seek an application for an extension of the patent term on the '158 Patent and rely at least in part upon the activities of 3M before the Federal Food and Drug Administration ("FDA"). The product covered by the '158 patent was subject to a regulatory review and subsequently approved by the FDA under PMA No. P010047, IDE No. G980283.

As required by 37 C.F.R. § 1.740(b), this supplement to the application for patent term extension under 35 U.S.C. § 156, including its attachment, is being submitted as an original and two duplicate copies thereof.

Please direct all inquires, questions and correspondence regarding this supplement to the undersigned.

The Director is hereby authorized to charge any additional fees which may be required for this submission or credit any overpayment to Deposit Account No. 50-0436.

Respectfully submitted,

N. Nicole Endejann, Reg. No. 50,229 and
Raymond A. Miller, Reg. No. 42,891

PEPPER HAMILTON LLP
One Mellon Center, 50th Floor
500 Grant Street
Pittsburgh, PA 15219
Phone: (412) 454-5869
Fax: (412) 281-0717
E-Mail: millerra@pepperlaw.com
Date: April 8, 2010

3M Health Care Business
3M Infection Prevention

3M Center, Bldg. 0275-04-E-01
St. Paul, MN 55144-1000
651 733 1110

3M

April 5, 2010

David M. Renzi
President and CEO
Neomend, Inc.
60 Technology Drive
Irvine, California 92618

Re: Neomend, Inc. – U.S. Reissued Patent No. RE38,158
Application for Extension of Patent Term under 35 U.S.C. § 156

Dear Mr. Renzi:

Congratulations on the recent approval by the Federal Food and Drug Administration (FDA) in the United States of Neomend's PMA No. P010047 for ProGel™ Pleural Air Leak Sealant on January 14, 2010. This letter confirms our understanding that the PMA No. P010047 was originally submitted by 3M Company on October 30, 1998 and references IDE No. G980283.

This letter also confirms that, in the event an extension of U.S. Reissued Patent No. RE38,158 ("the '158 Patent") now assigned to Neomend, Inc., under 35 U.S.C. §156, based on agency review to approve commercialization of ProGel™ Pleural Air Leak Sealant, may be obtained, 3M, and its affiliates and predecessors, including 3M Company, d/b/a 3M Health Care, and 3M Innovative Properties Company , (hereinafter "3M") hereby authorizes Neomend, Inc. to seek an application for an Extension of the patent term of its '158 Patent, relying at least in part upon the activities of 3M before the FDA.

Very truly yours,

Mark Schroer
Vice President – Business Development
3M Infection Prevention Division